INFLUENCE OF EXOME SEQUENCING RESULTS ON CAREGIVER ADAPTATION AND REPRESENTATIONS OF NEURODEVELOPMENTAL DISORDERS

by
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ABSTRACT

Background: Technology is evolving to detect and facilitate interpretation of genomic variants associated with neurodevelopmental disorders (NDD). With a current diagnostic yield of 25-40%, exome sequencing (ES) is postured to become a first-tier testing strategy for individuals with NDD. However, the psychological sequelae for caregivers of children with NDD following genetic testing are still poorly characterized, as are the ways their experiences may differ by the type of ES results returned. Past research shows that parental cognitive appraisals related to a child's medical or developmental condition (illness representations) are predictive of behavioral and psychological outcomes. This suggests that illness representations may shape caregivers' trajectories following genetic testing, including the process of adapting to their child's NDD.

Objective: Our study aimed to characterize the ways in which types of ES results affect caregivers' perceptions of their child's NDD and uncertainty about their child's health. We also aimed to describe how appraisals of the NDD influence caregivers' psychological adaptation and emotional distress, and to delineate the role of time in these relationships.

Methods: A total of 1,151 caregivers of children who had undergone ES for an NDD were contacted to participate in an online survey. Participants were recruited through two pediatric genetics clinics in Baltimore.

Results: A total of 190 participants completed the survey. Caregiver perceptions of treatment control and coherence significantly differed across categories of ES results (positive, negative, or VUS), as did overall uncertainty and several domains of uncertainty. Trends in the data indicated that caregivers' greater sense of personal control over their child's NDD, weaker unfavorable feelings associated with the NDD, and receiving a VUS vs. a negative ES result are associated with better adaptation. Negative emotion associated with the NDD was the only significant

predictor for the emotional distress outcomes. No association was found between time and the other variables of interest.

Discussion: This study deepens our understanding of caregivers' cognitive, affective, and adaptive processes following the disclosure of results from ES. Findings from this study carry implications for pre- and post-test genetic counseling, enabling clinicians to better tailor information, resources, and counseling interventions to families with NDD.

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BACKGROUND

Genetics of Neurodevelopmental Disorders

Neurodevelopmental disorders (NDD) are a heterogeneous group of conditions characterized by impairments in cognitive, motor, and/or social functioning. Disorders in this group typically manifest within the first few years of life and encompass autism spectrum disorder (ASD), global developmental delay (GDD), intellectual disability (ID), attention deficit hyperactivity disorder (ADHD), communication disorders, motor disorders like cerebral palsy, and specific learning disorders (Blesson & Cohen 2019). These disorders lie along a continuum of developmental brain dysfunction (DBD) and are diagnosed based on clinical criteria. NDD are relatively common in the United States pediatric population, with an estimated prevalence of 1 in 100 to 1 in 33 (1-3%) for GDD/ID (Blesson & Cohen 2019). A surveillance report by the CDC in 2014 found that 1 in 59 (1.68%) children at age 8 have an ASD diagnosis (Baio 2014).

From an etiological standpoint, NDD are understood to arise from the interaction of genetic and environmental factors in the developing brain (Blesson & Cohen 2019). NDD are highly heritable, as evidenced by sibling and twin studies; the heritability of ASD is thought to be as high as 80 to 90% (Johnson et al. 2011, Sandin et al. 2017). NDD are exceedingly genetically heterogeneous, manifesting as a clinical feature of a range of genetic syndromes. Genetic testing encompasses a multitude of methods including chromosome microarray analysis (CMA) and, more recently, exome sequencing (ES). ES is a test that analyzes the protein-coding regions (exons) of nearly all 20,000 genes in the human genome to determine if there are changes related to the patient's phenotype. Generally speaking, genetic testing results are categorized as positive/diagnostic (a causative variant was identified), negative/uninformative (no causative variant was identified), or of uncertain clinical significance (VUS) (insufficient

information to determine the variant's contribution to symptoms). In practice, a VUS is treated clinically as a negative result in that no causal diagnosis was obtained.

As genetic testing technology evolves in sensitivity and sophistication, so improves the ability to detect genetic aberrations leading to NDD. Currently, the diagnostic yield of ES for NDD is in the range of 25% to >40% (Rossi et al. 2017; Blesson & Cohen 2019). Data suggest that the yield is higher for individuals with an ID diagnosis than for those with ASD (Chérot et al. 2017). Genetic testing in NDD has the potential to establish a definitive etiological diagnosis, provide information about prognosis, guide medical management, determine inheritance pattern and associated recurrence risks, and, in some cases, may enable interventions targeted to the individual (Johnson et al. 2011; Reiff et al. 2015; Sawyer et al. 2016). Given its demonstrated diagnostic success, some researchers uphold ES as a superior first-tier clinical genetic test for NDD that may soon supplant CMA (Blesson & Cohen 2019; Srivastava et al. 2019).

Significance of Genetic Diagnosis for Families of Children with NDD

Hope for an underlying genetic explanation or diagnosis is oftentimes the driving force to pursue genetic testing (Griesemer et al. 2019). A positive test result can truncate a lengthy diagnostic odyssey and signify a point of inflection for families seeking the "why" for their child's illness. Adults with undiagnosed conditions seeking exome sequencing for themselves have noted that, in addition to uncovering an explanation for the disorder, a genetic diagnosis can provide a label, prognostic and treatment information, and pathways to support (Neustadt 2019). Evidence suggests that for many families, a conclusive diagnosis promotes acceptance of the condition, leads to increased understanding of the child's capabilities and potential, and legitimizes the family's experience (Reiff et al. 2015; Makela et al. 2009).

In the NDD realm, a developmental diagnosis (e.g., global developmental delay) is distinct from a genetic or etiological diagnosis (e.g., pathogenic variant in the *CUX1* gene). Studies of families with ASD show that having a clinical diagnosis of ASD does not preclude an interest in genetic testing. The majority of respondents in several quantitative surveys and interview-based studies of parents of children with ASD reported that they would follow through with testing if it were available for their affected child (Chen et al. 2013; Johannessen et al. 2017; Hanish et al. 2018; Wagner et al. 2019) or for the child's unaffected siblings (Narcisa et al. 2012). In one study, the highest proportion of parents were driven by the possibility to uncover a causal explanation for NDD (76%) (Johannessen et al. 2017). In another study, improved quality of healthcare and improved access to services were cited as highest perceived benefits of genetic testing for ASD (Lucas 2020). Validation, securement of school and early intervention services, and reproductive information (e.g., recurrence risks) are recurrent themes of psychological and practical benefits derived by parents who receive a genetic diagnosis for their child with NDD (Makela et al. 2009).

Nevertheless, even caregivers of children who get a genetic diagnosis acknowledge the sometimes limited utility of genetic testing. Participants in one qualitative study, which interviewed parents of children with ASD receiving a diagnosis through CMA, shared that positive results had no effect on existing therapeutic services and provided no further information than what they already knew about their child through the parenting experience (Reiff et al. 2015). Even if a diagnosis is desired, some ambivalence about genetic testing may manifest as fear for insurance discrimination and heightened concern for the child's future (Johannessen et al. 2017).

By that same token, research with families affected by neurological or neuro-developmental conditions suggests that clinically uninformative results do not universally connote disappointment and finality. Data from interview studies reveal that parents' responses to negative ES are layered and nuanced, encompassing gratitude for the experience, longing for continued research efforts, and hope for future changes in interpretation of the result (Krabbenborg et al. 2016; Skinner, Raspberry & King 2016).

VUS represent a subset of uninformative results that may be especially frustrating to parents, in which a DNA alteration is found but its connection to the child's disorder is unclear. A handful of past studies have examined how these "gray area" results from genetic testing are interpreted and internalized by the recipient. For the most part, individuals demonstrate good understanding and recall of their VUS results (Jez et al. 2015; Li et al. 2018), and report no changes to their child's care or ability to care for their child (Li et al. 2018). However, past research suggests that some people in this group may tend to exaggerate the actionable meaning of their VUS and mentally inflate the risk it confers, as was found in a survey of cancer patients (Bonner 2017). Parents may hold in tension contradictory interpretations that regard VUS as offering an answer and yet little clarification, perhaps exposing some degree of cognitive dissonance (Jez et al. 2015; Kiedrowski et al. 2016; Werner-Lin et al. 2017).

Reports from other disease populations contribute additional insights that have not emerged to date from NDD research. A longitudinal interview study with parents of pediatric cancer patients found that some interpreted non-diagnostic results from ES absolved them of guilt and reassured them that their child and relatives aren't at higher risk of other genetic conditions (Malek et al. 2017). Parents interviewed from cardiac arrhythmia, platelet dysfunction, and hearing loss cohorts perceived negative ES results as an opportunity for

improved disease management, even in the absence of diagnosis or new treatment guidance (Werner-Lin et al. 2017). As such, the same type of objective genetic testing result is valuated differently across recipients, and these ascribed meanings may well shape how families think about their child's condition.

Caregiver Illness Representations of NDD

Cognitions play an important role in individual and relational functioning. Cognitive processes directly relate to decision-making, coping behaviors, affective responses, and stress (Mire et al. 2018). These relationships have begun to be explored in individuals with NDD. A recent study from Israel found that mothers who held coherent, multifaceted beliefs about their children with ASD (i.e., those that incorporate both the child's strengths and challenges) displayed greater emotional availability in their parenting relationships (Sher-Censor et al. 2017). Other research with families with ASD supports a link between parents' sense of coherence, perceived locus of control, and parenting stress (Sivberg 2002; Hassall, Rose & McDonald 2005; Falk, Norris & Quinn 2014). As such, interrogating how caregivers perceive their child's NDD is likely to shed light on the interplay of cognitions and overall well-being in these families.

Leventhal's Common Sense Model of Self-Regulation, also known as the Self-Regulatory Model of Illness Representations, outlines how conceptualization of illness, coping, and emotional/behavioral outcomes relate in bidirectional pathways. According to this model, in response to illness, individuals construct parallel cognitive and affective representations that then influence coping efforts and outcomes (Leventhal et al. 1984, 2001). In Leventhal's classic conceptualization, cognitive illness representations comprise five components: *identity, timeline, cause, control/cure,* and *consequences* (Moss-Morris et al. 2002). Although NDD are not characterized as illnesses in the United States, they share attributes with chronic and life-long

medical conditions (Mire et al. 2018). Parents of children with NDD are embedded in many of the same health systems as families navigating a chronic diagnosis. Given that the starting point of Leventhal's model is a health-related stressor, it is reasonable to apply this theoretical framework to explore the well-being of parents raising a child with an NDD.

Research on NDD illness representations within Leventhal's proposed dimensions is limited. However, the *cause* dimension is probably the most widely examined. Caregivers' causal attributions for NDD in their children are varied and often multifocal. These attributions can include genetics/heredity, divine will, neurostructural differences, toxins in vaccines, and environmental pollutants. In one study, parents who categorized their child's ASD as regressive and witnessed a loss of skills were more likely to endorse environmental or external mechanisms as responsible (Goin-Kochel et al. 2015). Importantly, there is evidence that causal beliefs about ASD predict choice of treatment and behaviors related to health management (Al Anbar et al. 2010; Dardennes et al. 2011). Along the *timeline* dimension, a quantitative study using a nationally representative, CDC-administered survey of caregivers of children with developmental conditions found a positive association between endorsement of chronicity ("my child's condition is lifelong") and reported peer and conduct challenges among their children with ASD (Haney, Houser & Cullen 2018). Parents of children with ASD who participated in a mixed methods study expressed a range of views on the timeline/course and *controllability* of their children's symptoms, including hopes for a cure for ASD and a societal shift toward greater acceptance. Contrary to the researchers' hypothesis, the study found a positive association between parents' perceived personal control over their child's symptoms and levels of depression (Dale, Jahoda & Knott 2006).

Biomedical information, such as genetic testing results, can directly shape an individual's illness representations. This point was illustrated by Reiff and colleagues (2017) in a mixed methods study of parents of children with ASD ($N = 57$). The study assessed differences in beliefs about etiology and prognosis among parents who did and did not receive diagnostic/pathogenic CMA results. Although parents did not diverge significantly in their causal attributions, those whose children's testing uncovered a pathogenic variant perceived ASD as more permanent than those in which no genetic diagnosis was made (VUS or negative result). Across testing outcome groups, permanence ratings were positively correlated with perceived genetic contribution to ASD. Participant interviews revealed that parents whose children had negative or uncertain results tended to construe their children's symptoms as more controllable (modifiable) and amenable to improvement (Reiff et al. 2017).

As indicated in the studies outlined above, signs of a link between conceptualizations of NDD and genetic diagnosis have begun to surface, though evidence is still sparse and primarily focused on ASD over other types of NDD. To our knowledge, there are no studies that support the notion that genetic testing method (CMA vs. ES) differentially affects parental perceptions of their child's condition. However, it could be argued that children who get ES for an NDD indication have likely endured a longer wait to find a genetic cause than children who have just had CMA, and this wait time could influence perceptions. The current study attempted to support and expand on Reiff and colleagues' (2017) findings in a related but distinct caregiver sample (ASD + CMA testing vs. NDD + ES testing) to illuminate the downstream effects of NDD genetic testing. The sample in the current study reflected a growing number of families undergoing ES, which is projected to be the first-line test for NDD in the near future (Blesson & Cohen 2019; Srivastava et al. 2019). Furthermore, we set a target sample size more than triple

that of the sample in Reiff et al.'s study, which we hoped would allow us to capture a broader and perhaps more generalizable range of caregiver experiences within which to discern meaningful patterns between ES and NDD representations. We anticipated that any relationships found in the current study would be directionally congruent to those in the study by Reiff and colleagues.

Psychological Adaptation and Distress in NDD Caregivers

Adaptation is conceptualized as a "dynamic and multidimensional process of coming to terms with the implications of a health threat and the outcomes of that process" (Biesecker et al. 2013). This definition is rooted in Taylor's theory of cognitive adaptation (1983), which postulates that adaptation centers on three interrelated themes: searching for meaning, regaining mastery, and restoring self-esteem. It is through these processes that one can begin to appreciate the personal significance of the health threat (referenced in Lim & Chong 2017). Adaptation is sometimes referred to as *adjustment* or *acceptance* in other studies (Biesecker & Erby 2008), and comprises processes of positive inner growth and benefit finding (Lim & Chong 2017; Griesemer et al. 2019). Given that facilitating adaptation is regarded as an integral goal in genetic counseling work (Biesecker & Erby 2008), it is essential within the practice to better understand what upstream factors promote or hinder longer-term adaptation, in order to intervene where possible.

In their seminal Transactional Model of Stress and Coping, Lazarus & Folkman (1984) posit that adaptation is an outcome of coping, following primary and secondary appraisals of a stressor. The manner in which parents cope through problem management, emotional regulation, and meaning-making can either foster or hamper movement toward adaptation. This component of Lazarus and Folkman's model has been explored extensively in family systems within the

NDD literature. Coping strategies like reframing and positive reappraisal (both part of meaning-based coping), self-empowerment, and focus on family integration have been linked to reduction of parental stress in several studies of children with developmental disabilities (Jones & Passey 2004; Werner & Shulman 2013; Minnes, Perry & Weiss 2015). Parental coping strategies can also be dynamic, evolving over time as the child ages (Gray 2006). Importantly, research in families with NDD supports coping response as a robust predictor of adaptation, whereas characteristics of the child's condition are not reliably predictive (severity of symptoms, level of functioning, maladaptive behaviors) (Pianta et al. 1996; Minnes, Perry & Weiss 2015).

Although psychological well-being in parents of children with NDD has garnered research attention (e.g., Cramm & Nieboer 2011; Werner & Shulman 2013), direct measurement of adaptation in this population is scant. However, a construct analogous to adaptation, used by several researchers, is parents' resolution (acceptance) of a clinical diagnosis. Resolution refers to successful integration of pre- and post-diagnosis internal representations of the child and the self (Milshtein et al. 2010). Milshtein and colleagues found that among mothers in their sample, the only significant correlate of resolution status was perceived negative impact of the child's ASD diagnosis on the family.

Like adaptation, psychological distress and well-being are also important constructs for examining how families assimilate the challenges of NDD. These indicators of psychological adjustment have been captured through outcomes commonly evaluated in social science research, including quality-of-life measures. Raising a child with a disability poses cognitive, emotional, and physical demands on the family (Milshtein et al. 2009). Many studies have demonstrated higher rate of stress, depressive symptomology, and poor psychological well-being among parents of children with NDD compared to the general population (Byrne et al. 2010;

Cheshire, Barlow & Powell 2010; Cantwell et al. 2015; Padden & James 2017; Stewart et al. 2017; Lee & Chiang 2018). A 2010 review showed that parents of children with intellectual and developmental disabilities frequently encounter chronic stressors, which may predict adverse physical and psychological health outcomes (Miodrag & Hodapp 2010). There is evidence to suggest that parents of children with ASD are more likely to experience anxiety disorders (Conner, Maddox & White 2013) and clinically significant psychological distress (Gatzoyia et al., 2014). Furthermore, a meta-analysis (Hayes et al. 2013) and a cross-sectional study (AlAnsari & Jahrami 2018) found that parents of children with ASD experienced greater stress than parents raising children with typical development or with other types of NDD. Importantly, parenting stress has been associated with lack of diagnosis resolution, implying that persistent stress is inversely related to adaptation, potentially as an indicator of ineffective coping in the parent dyad (Sheeran, Marvin & Pianta 1996).

Evidence also supports an influencing role for illness representations in psychological distress in parents of children with ASD. Gatzoyia and colleagues (2014) found that parents with strong beliefs about the chronicity and consequences of their child's ASD had more severe depressive symptoms and general psychological distress. This NDD-specific result is consistent with conclusions from a prior meta-analytic review (Hagger & Orbell 2003). This review compiled 45 empirical studies based on Leventhal's Common Sense Model of Illness Representations, identifying seven categories of coping strategies and six categories of health outcomes. Hagger and Orbell found that the illness representation dimensions of consequences, timeline, and identity were all significantly negatively associated with psychological well-being, as well as role and social functioning. In addition, the various dimensions of illness representations were correlated with different coping strategies. Perceived controllability was

related to expressing emotions and problem-focused coping, while perceived chronicity was related to avoidance and emotional coping. This meta-analysis supports a role for illness representations not only in Leventhal's theoretical model, but also Lazarus and Folkman's conceptualization of coping and adaptation.

Time in Illness Appraisals and Adaptation

Few studies have examined the role of time in influencing the variables in the pathway of interest, namely, illness representations and psychological adaptation. Interestingly, evidence from a quantitative multi-time point study points to the shifting salience of genetic test results on parental cognitions outside of the context of NDD. This study found that at 12 months, parents who received a VUS on a prenatal CMA perceived their children as less competent than parents who received normal/likely benign results. However, this difference vanished at 36 months (Desai et al. 2018). One would imagine that illness representations would change with time, particularly those related to the chronic and cyclical nature of the condition. Time and experience generate data points that bolster or threaten ideas that an individual has constructed about the condition. However, no research to date has investigated this assumption within NDD populations.

Adaptation is a process that occurs over the course of time, and indeed, most individuals do adapt to the challenges associated with a genetic condition or risk (Biesecker, Peters & Resta 2019). No studies have examined through longitudinal or cross-sectional approaches how psychological adaptation changes over time or relates to time since diagnosis or testing. Past research with parents of children with chronic health conditions generally indicates that resolution status is not a function of time since diagnosis (Popp et al. 2014; Milshtein et al. 2010). For example, Popp and colleagues (2014) found no difference in time since diagnosis

between parents of children with type 1 diabetes or asthma who were unresolved, and those who were resolved. In this study, time since diagnosis ranged from 18 to 36 months, and 41% of parents were unresolved with their child's diagnosis at the time of study participation. Furthermore, several longitudinal studies have found that resolution is unstable among parents of children with ASD and CP, fluctuating rather than progressively increasing (Yirmiya et al. 2015; Rentinck et al. 2010). Popp suggests that resolution may be a coping strategy in response to stress, and thus may not even be a viable proxy for psychological adaptation as the current study examines it (Popp et al. 2014).

Uncertainty in NDD Caregiving

Uncertainty permeates the experience of living alongside a chronic condition or disability. For these families, feelings of uncertainty can stem from fluctuations in the child's health and functional status, transitional periods of renegotiating independence and caregiving roles, questions of prognosis and life expectancy, changes to treatment access or eligibility, and anticipated loss of support sources (Pryce et al. 2017; Jivanjee, Kruzich & Gordon 2009; Dodgson et al. 2000). From a theoretical standpoint, uncertainty has been extensively described by Mishel, who defines it as "the inability to structure the meaning of illness related events" (Mishel 1988, 1990). According to her theory, uncertainty is not a desirable or undesirable state per se, but is appraised as either a danger or an opportunity (Mishel 1990). More recently, Han and colleagues (2011) have elaborated on Mishel's work in a taxonomy of uncertainty in healthcare, positing that the nuanced experience of uncertainty can be mapped along three dimensions: *issue* (scientific, practical, personal), *source* (probability, ambiguity, complexity), and *locus* (patient vs. clinician) (Han, Klein & Arora 2011).

In the realm of clinical genetics, desire to alleviate illness-related uncertainty can be a potent motivator for genetic testing (Baum, Friedman & Zakowski 1997; Khan et al. 2016). Indeed, research findings imply that a diagnosis may confer psycho-emotional advantages in the process of adapting to living with a condition in the family. Parents of children with undiagnosed medical conditions have been found to have lower perceived social support, hope, coping efficacy, and psychological adaptation, compared to parents of diagnosed children (Yanes et al. 2017). Similarly, mothers of children with etiologically unexplained intellectual disability scored higher on measures of anxiety, emotional strain, and worry, compared to mothers of children with Down syndrome or no disability (Lenhard et al. 2005). That said, even when a genetic diagnosis is known, uncertainty often persists, especially when knowledge about a condition is lacking due to its novelty or rarity. In contrast to the findings described above, qualitative investigations suggest that parents who obtain a diagnosis for their child may have similar expressions of and responses to uncertainty as those without a diagnosis (Hayeems et al. 2016; Reiff et al. 2012). Much of this uncertainty centers on the child's current and future health, and prognostic information (Hayeems et al. 2016; Inglese et al. 2019). Furthermore, there is evidence of association between higher uncertainty and higher quality of life in ASD families, partially mediated by the parental sense of mastery over the disorder (Garrett 2014). It appears that characteristics of uncertainty and its appraisal, not just its presence or absence, are important determinants in adaptation following genetic testing.

It is suggested that uncertainty is related to parental cognitions about their child's illness and constitutes another layer of appraisals, although it is not explicitly captured in validated measures of illness perceptions (i.e., the Illness Perception Questionnaire (IPQ)). Madeo and colleagues (2012) found that uncertainty was associated with perceived disease severity, which

could be construed as analogous to the *consequences* dimension of illness representation (Madeo et al. 2012). Uncertainty also bears on coping strategies (Macnamara 2014) and interacts with caregivers' dispositional factors like optimism and hope (Macnamara 2014; Bell et al. 2019) to influence how families come to terms with a child's condition. Uncertainty in children's illness has also been linked to adverse psychological outcomes including depression, anxiety, and cognitive disturbances (Yanes et al. 2017). Given this established relationship between uncertainty, adaptation, psychological distress, and potentially illness representations, it is important to take uncertainty perceptions into account by studying the impact of pediatric-onset NDD and genetic testing.

Conceptual Framework

As alluded to in the preceding section, Leventhal's Self-Regulatory Model of Illness Representation (SRMIR) and Lazarus and Folkman's Transactional Model of Stress and Coping (TMSC) jointly form the basis of the present study's conceptual framework. In both of these models, a stressor or stimulus (such as results from ES) is appraised by an individual; these appraisals have cognitive and affective dimensions. We conceptualize these appraisals of ES results as bearing on primary appraisals of the child's NDD (illness representations and uncertainty), which in turn guide coping mechanisms. Per the TMSC, this coping process leads to adaptation and other downstream psychological and adverse affective outcomes in the form of anxious and depressive symptoms.

Although it doesn't appear in the classic SRMIR and TMSC theoretical models, uncertainty may act as another cognitive force shaping illness representations. Previous research has integrated Mishel's characterization of uncertainty (1988) as a process intersecting with Lazarus and Folkman's appraisal-coping-adaptation pathway (Macnamara 2014). In addition, the

time that has elapsed since the genetic testing is expected to affect the coping process and consequently psychological adaptation and distress.

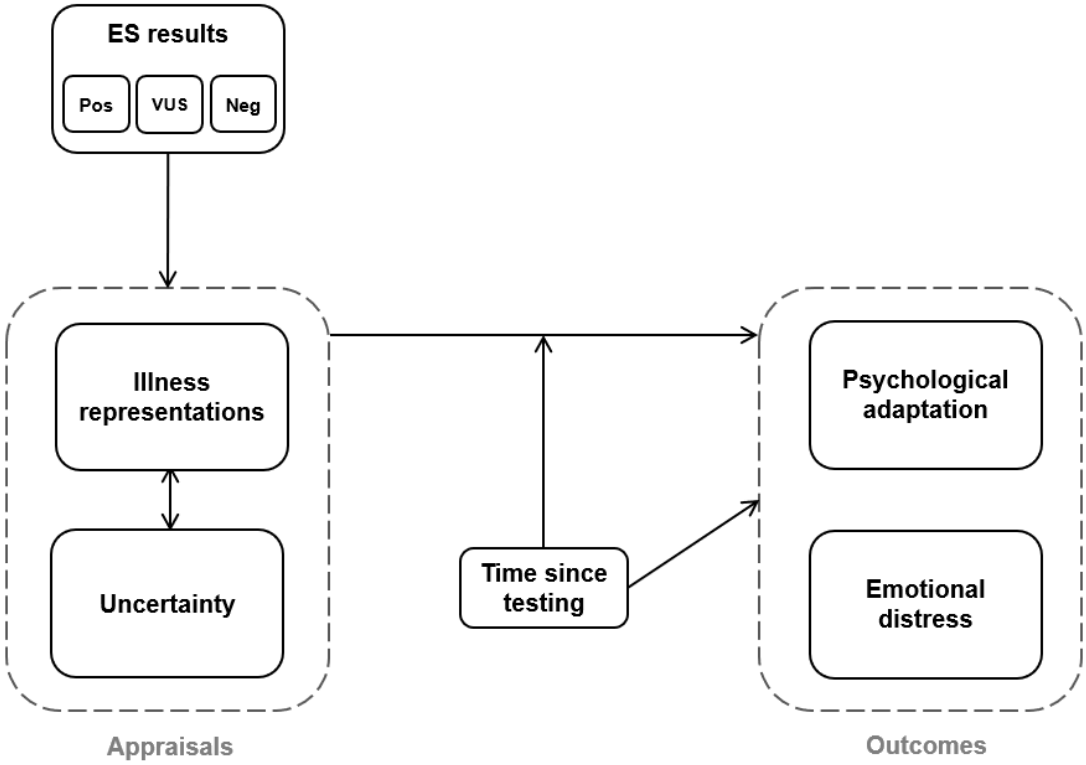

Figure 1. A conceptual framework for the influence of exome sequencing results on representations of NDD and psychological adaptation. In this proposed model, the category of the child's ES results contributes to caregivers' psychological adaptation by shaping illness representations related to the NDD. Time also plays a role in appraisals and outcomes. ES = exome sequencing; Pos = positive; VUS = variant of uncertain significance; Neg = negative.

Significance

To date, we are unaware of any studies that have proposed and tested interlocking relationships between genetic testing outcomes, illness representations, and psychological adaptation among parents of children with NDD. Studies that have examined pieces of the proposed adaptation pathway have largely depended on qualitative methodology (Dale, Jahoda & Knott 2006; Gray 2006; Kiedrowski et al. 2016; Krabbenborg et al. 2016; Reiff et al. 2017; Skinner, Raspberry & King 2016; Werner-Lin et al. 2017; Li et al. 2018). Furthermore, the bulk of existing research has focused on only one type or group of diagnoses within NDD, predominantly ASD, which limits generalizability of findings. By surveying parents of children across the NDD spectrum, we hope to capture a breadth of parent experiences at different post-test time points and elucidate relationships across a number of measures. As genetic testing for NDD increasingly moves toward utilization of ES, it will be of paramount importance to gain insight into the cognitive and emotional trajectories of families as they adapt to a definitive genetic diagnosis or lack thereof. We hope this study will contribute to the development of more effective and timely interventions for families susceptible to poorer psychological adjustment after the genetic testing experience.

OBJECTIVE AND STUDY AIMS

Empirical studies of caregivers to children with NDD has largely focused on indicators of psychological and emotional wellbeing. Some studies have also linked these outcomes to caregivers' cognitive and emotional representation of their child's condition. The current study aims to connect these pieces to genetic results from ES, which we propose may be an upstream predictor of illness appraisals, coping, and adaptation. We also sought to understand how ES results contributed to caregivers' uncertainty related to their child's NDD. By expanding on the existing knowledge base in these domains, we hope genetic counselors and other healthcare providers can better anticipate the needs of families and tailor their counseling work accordingly.

Aim 1: To assess how type of result from child's exome sequencing (ES) relates to caregiver illness representations of NDD and uncertainty.

Hypothesis 1.1: Certain illness appraisals of NDD among caregivers will be sensitive to genetic testing and will differ based on the category of ES results their child received:

- Permanence (chronicity) will be highest in the positive ES results group, followed by the VUS group, then the negative ES results
- Controllability (personal and treatment control) will be highest in the negative ES results group, followed by the VUS group, then the positive ES results group
- Coherence will be highest in the positive ES results group, followed by the VUS group, then the negative ES results group
- Attribution to a genetic cause will be highest in the positive ES results group, followed by the VUS group, then the negative ES results group

- Uncertainty about their child's health will be highest in the VUS group, followed by the negative ES results group, then the positive ES results group

Hypothesis 1.2: Caregiver uncertainty about their child's condition will moderate the relationship between type of ES results and illness representations.

Aim 2: To describe the extent to which illness appraisals among caregivers of children with NDD predict psychological adaptation and emotional distress.

Hypothesis 2.1: Caregivers who view their child's NDD as more permanent, less controllable, less coherent, more emotionally distressing, carrying greater consequences, and/or experience greater uncertainty about their child's health will have poorer psychological adaptation and greater emotional distress.

Aim 3: To examine the role of time in caregivers' psychological adaptation and emotional distress.

Hypothesis 3.1: Caregivers who have greater temporal distance from genetic testing will be more adapted to their child's NDD than those for whom testing was more recent, controlling for other predictor variables.

Hypothesis 3.2: Time will moderate the relationship between illness appraisals and adaptation.

METHODS

Study Design

Our cross-sectional study used a web-based survey instrument to examine illness representations and psychological adaption in caregivers of children with NDD. Prospective participants were recruited in a targeted manner through genetics clinics at two medical institutions in Baltimore, Maryland: Kennedy Krieger Institute (KKI) and Johns Hopkins Medicine (JHM). Participants completed an online survey comprising several validated measures of constructs within the conceptual framework. The survey was built using the Qualtrics platform, licensed for use by students at Johns Hopkins Bloomberg School of Public Health. Estimated time to complete the survey was 15 to 25 minutes. Participants who completed the survey were eligible to receive a $5.00 electronic gift card.

Pilot Study

A pilot study was conducted before the main study was distributed. The purpose of this pilot study was to ensure that the questions and instructions on the survey were clear to participants, as well as to provide an estimated time to complete the survey. Pilot participants were asked to complete the survey and provide feedback by responding with any questions or comments about the survey. Two caregivers who met inclusion criteria for the main study were recruited from the KKI Department of Neurology and Developmental Medicine by genetic counselor Julie Cohen and participated in the pilot study. The pilot study resulted in no changes to structure or wording of the survey questions.

Recruitment

Six study co-investigators at KKI and JHM (Julie Cohen, Rebecca McClellan, Weiyi Mu, Krista Schatz, Kelsey Stauff Guthrie, and Carolyn Applegate), who are all clinical certified genetic counselors, provided the student investigator with access to logbooks of their patients. Visit dates for the logbooks ranged from 2012 to 2020. These included patients for whom ES was ordered. The student investigator then analyzed patient charts through the electronic medical record to determine if the patient, and by extension their caregiver(s), met eligibility requirements for the study. If the patient met any of the following conditions, they were omitted from recruitment: 1) deceased, 2) non-English speaking, as denoted by an interpreter request in the chart, 3) no documentation of ES results received from the lab, 4) genetic counseling note did *not* include NDD in the indication for testing or reason for referral, 5) autonomous (no caregiver or guardian listed), 6) duplicate contact (same patient or affected sibling of a patient already listed for contact), 7) secondary (incidental) finding was returned on ES.

If a patient met inclusion criteria, the contact email address and/or home address listed in the electronic medical record was recorded. Once a prospective participant list was compiled from each genetic counselor's patient pool, study invitations were sent out by email or physical mailing (see **Appendix D**). For those patients that had an email address on file, a mail merge was created with the study invitation and deployed in batches. For KKI patients, the student investigator emailed the study invitations from an email address created specifically for the study, NDD-Genetics-Study@kennedykrieger.org. For JHM patients, each co-investigator emailed the study invitations to her respective list of patient contacts.

Following survey completion, electronic gift cards were distributed to respondents who supplied their email addresses in the gift card form linked at the end of the main survey.

Study Sample

Study participants were self-identified primary caregivers to an individual who underwent genetic counseling and clinical exome testing between 2012 and 2020, and had these test results returned to them. The affected individuals were living and had a documented clinical diagnosis of a pediatric-onset NDD, either isolated or part of a broader diagnosis or disease presentation, as the indication for exome sequencing. For the purposes of this study, "neurodevelopmental disorder" encompassed global developmental delay (GDD), intellectual disability (ID), autism spectrum disorders (ASD), and cerebral palsy (CP). Inclusion criteria also specified that respondents be at least 18 years of age. There were no eligibility restrictions based on demographics such as race, ethnicity, sex, or gender.

The proposed sample size for the study was 200 individuals. Two power calculations for linear bivariate regression analyses were conducted to specifically assess the relationship between illness representations and psychological adaptation (Aim 2) (see **Tables 1 and 2**). Holding alpha at 0.05 and power at 0.80, a small ($r^2 = 0.01$) to medium ($r^2 = 0.09$) effect size for the effect of illness appraisals on adaptation was deemed reasonable for this study (Cohen 1992).

Table 1. Sample size required to achieve 80% power to detect small and medium effect sizes with 10% variance explained by all other covariates in the regression model

	Total N	Alpha level (α)	Number of Covariates	% Variance Explained by Key Variable (Partial r^2)	% Variance Explained by All Other Covariates	Power (1-β)
1	348	0.05	12	2	10	0.80
2	171	0.05	12	4	10	0.80
3	136	0.05	12	5	10	0.80
4	83	0.05	12	8	10	0.80
5	54	0.05	12	12	10	0.80

Table 2. Sample size required to achieve 80% power to detect small and medium effect sizes with 5% variance explained by all other covariates in the regression model

	Total N	Alpha level (α)	Number of Covariates	% Variance Explained by Key Variable (Partial r^2)	% Variance Explained by All Other Covariates	Power (1-β)
1	367	0.05	12	2	5	0.80
2	181	0.05	12	4	5	0.80
3	144	0.05	12	5	5	0.80
4	88	0.05	12	8	5	0.80
5	57	0.05	12	12	5	0.80

Measures

A copy of the complete survey instrument is provided in **Appendix E.**

Eligibility Screening

After reading the informed consent form (see **Appendix C**), participants were asked a series of five questions as an additional precautionary measure to ensure that they fulfilled inclusion criteria. These questions were: 1) "Are you the primary caregiver to an individual with a neurodevelopmental disorder?", 2) "Is this individual still living?", 3) "Are you 18 years or older?", 4) "Were you invited to participate in this study by a genetics provider at Kennedy Krieger Institute or Johns Hopkins Medicine?", and 5) "To your knowledge, has anyone else in your household already completed this survey?" If they responded "No" to Q1, Q2, Q3, and/or Q4, they were automatically redirected to the survey end page. Participants who responded "Yes" to Q5 were also redirected.

Demographics

Participants were asked a series of nine close-ended, multiple-choice questions about their current age, gender, race, ethnicity, marital status, employment status, and level of education.

Impact of COVID-19

Participants were asked a series of six close-ended, multiple-choice questions about how the global COVID-19 (novel coronavirus) pandemic affected their day-to-day life, including shelter-in-place status, caregiving activities, financial situation, and continuity of services for their child. These questions were designed to help determine analytically if COVID-related changes to family life act as a potential confounder for the study outcomes.

Respondent and Family Characteristics

Participants were asked 14 short open-ended, multiple-choice, and binary yes/no questions about their caregiving role, their affected child, the child's medical and behavioral history, and other family members. Respondents were instructed to answer all survey questions for their oldest child with NDD who had undergone ES. One of these questions, "Did you already receive results from your child's exome testing?", served as an additional screener question. If participants responded "No" to this question, they were automatically redirected to the survey end page.

Exome Sequencing

Participants were asked five short open-ended, multiple-choice, and 5-point Likert scale questions (1 = "not at all" to 5 = "completely") about the results from ES and the perceived extent to which the test result explains their child's neurodevelopmental differences. A central predictor variable, "time since ES," was calculated by subtracting the child's reported age at the time of ES from the child's current age. "Time since clinical attention" was calculated by subtracting the child's reported age at the time the caregiver sought out a specialist from the child's current age.

NDD Characteristics

Participants were provided a list of eight developmental diagnoses and NDD-related symptoms and asked to indicate which described their child. This list was developed for the current study and selected based on definitions of NDD in the literature (e.g., American Psychiatric Association 2013; Srivastava et al. 2019) and in consultation with genetic counselor and committee member Julie Cohen. A total score was calculated by tallying the number of symptoms that the respondent checked off.

In addition, participants were provided a list of 19 cognitive, communication/ interpersonal, mobility, sensory, and self-care difficulties items and asked to indicate which described their child. These items were derived from a validated measure of disability in childhood, About My Child—19-Item (AMC-19) (Williams et al. 2018). Finally, they were asked to report on the relative seriousness of their child's condition on a multiple-choice item.

Revised Illness Perception Questionnaire for Autism (IPQ-RA) (Al Anbar et al. 2010, Mire et al. 2018)

Participants were asked to respond to 57 items on a version of the Revised Illness Perception Questionnaire (IPQ-R) adapted and validated for parents of children with autism. The IPQ-RA consists of nine subscales each corresponding to a specific dimension of cognitive and emotional representations: 1) Identity, 2) Timeline: Acute/Chronic, 3) Consequences, 4) Personal Control, 5) Treatment Control, 6) Illness Coherence, 7) Timeline: Cyclical, 8) Emotional Representation, and 9) Causal Beliefs. For this study, the IPQ-RA was modified slightly to omit the Identity subscale, as features of the child's disorder were evaluated in a preceding section of the survey. Furthermore, Timeline: Acute/Chronic is referred to as "Chronicity" and "Timeline: Cyclical" as "Cyclicity" from this point forward for brevity. Items on all IPQ-RA subscales (except Causal Beliefs, see below) were measured on a 5-point Likert scale (1 = "strongly disagree" to 5 = "strongly agree"). Items 1, 4, 15, 17, 18, 19, 23, 24, 25, 26, 27, and 36 were reverse scored. A total score for each subscale except Causal Beliefs was calculated by summing the responses to the items within that subscale.

The causal beliefs subscale consists of 18 attributional items, which in scoring are grouped into categories of "Personal attribution," "Environmental attribution," and "Hereditary attribution" (Al Anbar et al. 2010). For analysis in the current study, total score from the

"Hereditary attribution" grouping was utilized, which consists of one causal attribution item, "Genetics / heredity".

Table 3. Description of IPQ-RA subscale interpretations†

IPQ-RA Subscale	Higher scores indicate that caregivers:
Timeline: Acute/Chronic (Chronicity)	Perceive symptoms of their child's NDD as chronic
Timeline: Cyclical (Cyclicity)	Believe their child's NDD is cyclical and unpredictable
Consequences	Experience/perceive negative consequences of NDD
Personal control	Perceive they have control over their child's NDD
Treatment control	Perceive they have control over treatments for their child's NDD
Coherence	Believe they understand their child's NDD
Emotional representation	Experience negative feelings associated with their child's NDD

† Adapted from Mire et al. (2018)

Parental Uncertainty about a Child's Health Scale (PUCHS) (Macnamara 2014)

Participants were asked to respond to a series of 30 items about their perceptions of uncertainty related to their child's NDD. The PUCHS measures several dimensions of parental uncertainty and weights each dimension by importance. In Part A, each of 15 uncertainty items is measured on a 5-point Likert scale ranging from -2 = "strongly disagree" to 2 = "strongly agree." Each item has the same stem "Having a genetic diagnosis or not having a diagnosis for my child's condition leaves me…" and asks respondents how much they agree with "insufficiently prepared to participate in treatment decisions for my child," "unsure what to tell relatives about risks to their children," "uncertain about the meaning of my child's life," etc. The prompt/stem for Part A was altered from the original PUCHS to accommodate participants who either have or lack a diagnosis. The original prompt read: "Not having a diagnosis for my child's condition leaves me…". Additionally, for analytic ease and clarity of reported data, PUCHS scores were re-coded on a scale from 0 to 4. Scores were transformed by adding 2 to the raw score, such that

a score of -2 became 0, a score of -1 became 1, and so forth. A score of 0 indicated lowest levels of uncertainty, while a score of 4 indicated highest levels of uncertainty. A similar re-coding scheme has been utilized in the past by Yanes and colleagues (2017).

In Part B, each importance item is also measured on a 5-point Likert scale ranging from 1 = "unimportant" to 5 = "important". The weighted total uncertainty score for each individual is calculated by weighing each uncertainty item by its corresponding importance and then dividing by the sum of the importance items (Macnamara 2014, Yanes et al. 2017). As described by Umstead et al. (n.d.), "Higher scores indicate a participant perceives greater uncertainty in important domains related to his or her child's condition."

The survey was deployed to participants with the original version of the PUCHS with 15 weighted items (30 total questions), as presented in the validation study by Umstead et al. (n.d.). The authors originally proposed seven dimensions of uncertainty: Diagnostic, Medical Management, Future, Reproductive, Family, Social, and Existential. Following their exploratory factor analysis, they reported that three weighted items were removed during model refinement due to weak correlation to other scale items: 4/b, 14/b, and 15a/b. The latter two weighted items comprised the entire Existential subscale. However, other contemporaneous and subsequent publications that have utilized the PUCHS differ in their factor loadings and delineation of uncertainty domains (Macnamara 2014; Yanes et al. 2017; Bell et al. 2019). Given these discrepancies, we left all original PUCHS items in the survey that was distributed to participants and conducted a factor analysis specific to this study, described in **Results**.

Psychological Adaptation Scale (PAS) (Biesecker et al. 2013)

Participants were asked a series of 20 items through the Psychological Adaptation Scale (PAS) to assess how they think about how the experience of caregiving for a child with NDD has made a difference in their lives. The PAS includes four subscales containing five questions each: 1) Coping Self-Efficacy, 2) Self-Esteem, 3) Social Integration, and 4) Spiritual Well-Being. Each item begins with the stem "Being a caregiver of an individual with an NDD has…". Items are measured on a 5-point Likert scale ranging from 1 = "not at all" to 5 = "very much." The score for each subscale was calculated by taking the average of items with the subscale. An overall score was calculated by averaging the four subscale scores. Higher scores reflected greater adaptation to the child's NDD.

To minimize framing effects or recency bias related to eliciting thoughts about uncertainty or adaptation, participants were randomized by the survey software to complete either the PUCHS or the PAS first, after the IPQ-RA and before the DASS-21 (see below). The order of all other survey sections remained static.

Depression Anxiety Stress Scales – 21 Items (DASS-21) (Lovibond & Lovibond 1995)

Participants were asked a series of 21 questions that assessed their experience of various emotional and behavioral symptoms of stress, anxiety, and depression in the past week. Each item is measured on a 4-point Likert-format scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much or most of the time). The scores for depression, anxiety, and stress were calculated by summing the relevant items for each.

Open-Ended Responses

Finally, participants were asked five questions to reflect on their experiences of exome testing in several short, free-form responses. The last of these invited them the opportunity to

share additional thoughts or comments with the study team. Participants were instructed not to disclose any identifying information about their child. These qualitative questions were included to serve descriptive purposes and to help contextualize surprising, inconsistent, or non-significant results from the quantitative analyses.

Statistical Analyses

Responses from the survey were analyzed to examine relationships between three main groups of predictors and outcomes. The first aim of the study was to examine how ES results relate to primary appraisals about the child's NDD. In our study, primary appraisals were illness representations and uncertainty about the child's NDD. These relationships were assessed using a series of one-way and two-way analyses of variance (ANOVA). The second aim of the study was to examine how NDD appraisals relate to psychological adaptation and emotional distress. Emotional distress constituted symptoms of depression, anxiety, and stress. These relationships were assessed using a series of binomial logistic regression models. The third aim of the study was to examine the relationship of time to the remaining variables. These relationships were assessed using a series of binomial logistic regression models. Statistical analyses were completed using IBM SPSS Version 25.

Descriptive Statistics

Frequencies and percentages were calculated to characterize the population based on demographics as well as characteristics of the ES testing, the child's diagnosis, the caregiver's role, and family structure. Mean values and standard deviations were calculated for numerical/scale variables, such as child's current age and age at testing. In addition, mean values and standard deviations of each subscale and full scale were calculated to characterize the

population based on illness representations, uncertainty about the child's condition, anxiety, depression, stress, and psychological adaptation.

ES results category was transformed into two dummy variables for use in subsequent regression analyses, with the VUS group serving as the reference group. Preliminary descriptive analyses were run to examine the relationship of ES levels with psychological adaptation and uncertainty. Because VUS emerged as an extreme for both variables (either highest or lowest mean out of the three ES results groups), it was selected as a suitable reference group. The dummy coding scheme for creating two new variables is shown below in **Table 4**.

Table 4. Descriptive statistics and dummy coding scheme for ES results [*N* = 190]

Outcome Variable	**ES Results Level**	***M***	***SD***
Psychological adaptation (PAS)	Positive	3.81	.68
	Negative	3.56	.79
	VUS	3.88	.73
Uncertainty (PUCHS (26 item))	Positive	1.32	.85
	Negative	1.76	.85
	VUS	1.92	.87

OutcomeES	**x1_RefVUS**	**x2_RefVUS**
Positive = 1	1	0
Negative = 2	0	1
VUS (reference) = 3	0	0

Note: x1_refVUS = difference in means between VUS and positive groups; x2_refVUS = difference in means between VUS and negative groups

Ethics Statement

This research study was determined to be exempt from human subjects review by the Institutional Review Board of the Bloomberg School of Public Health, Johns Hopkins University (JHSPH IRB #12189), on July 2, 2020. Participants were informed that reading a description of the study and clicking "I accept" to proceed to survey indicated their consent to the study. Documentation of written consent was waived by the JHSPH IRB. See **Appendix C** for informed consent language.

Funding

This study was supported by the Intramural Research Program of the National Human Genome Research Institute, National Institutes of Health.

RESULTS

Participant Characteristics

Recruitment

A total of 1,151 prospective participants were contacted by email or physical letter between September 2020 and December 2020. Of those who were invited to participate, 999 (86.8%) had children tested through Kennedy Krieger Institute and 152 (13.2%) had children tested through Johns Hopkins Medicine. A total of 254 (22.1%) respondents started the survey and 24 people did not continue beyond the eligibility questions either because they voluntarily quit, or because they were not eligible to proceed. Ten further respondents were directed to the end of the survey after responding negatively to screener Q3 ("Did you already receive results from your child's exome testing?").

Conservative requirements were set for the four validated quantitative measures such that responses were only included in analyses if participants completed at least 50% of the items of each subscale within the IPQ-RA, PUCHS, PAS, and DASS-21. The exact cutoff depended on the number of questions in each subscale. Thirty responses were excluded for failing to meet these requirements. For those who were retained, person mean imputation was utilized to impute missing data within the scales given each respondent's answers to other items in the subscale. At least one data point was imputed for 19 cases. The final sample comprised 190 eligible respondents (74.8% of the total who submitted a survey response, and 16.5% of those initially contacted).

Demographics

Of the 190 final participants, the majority were female (88.9%), white (85.3%), and non-Hispanic or Latinx (95.3%). The average age of participants was 43.8 years. The greatest proportion of respondents reported that they were employed full-time currently (49.5%) and before (54.7%) the COVID-19 pandemic. Respondents were highly educated, with 32.1% reporting a college degree and 41.1% reporting a graduate degree. Most (80.6%) were married. Demographic characteristics are summarized in **Table 5** below. Characteristics of the excluded respondents are not shown, but were comparable to characteristics of participants who were retained in the study sample.

Table 5. Participant demographics [$N = 190$]

Variable	Response	*N*	%
Gender	Male	21	11
	Female	169	89
Race (*check all that apply*)	American Indian/Alaska Native	1	0.5
	Asian	10	5.2
	Black/African American	16	8.4
	White	162	85.3
	Other	10	5.2
Ethnicity	Hispanic/Latinx	9	4.7
	Non-Hispanic/Latinx	181	95.3
Marital status	Married	153	80.6
	Divorced	10	5.2
	Widowed	8	4.2
	Single	9	4.7
	Partnered but not married	8	4.2
	Other	2	1
Current employment status	Employed, full-time	94	49.5
	Employed, part-time	28	14.7
	Unemployed	32	16.8
	Retired	13	6.8
	Student	2	1.1
	Other	21	11.1
Employment status before COVID-19	Employed, full-time	104	54.7
	Employed, part-time	30	15.8
	Unemployed	19	10.0
	Retired	12	6.3
	Student	5	2.6
	Other	20	10.5
Highest level of education	High school/GED	11	5.8
	Technical school	4	2.1
	Some college	36	18.9
	Completed college	61	32.1
	Graduate degree	78	41.1
Annual household income	Under $30,000	10	5.3
	$30,001 - $50,000	11	5.8
	$50,001 - $70,000	29	15.3
	$70,001 - $100,000	32	16.8
	$100,001 - $250,000	86	45.3
	Above $250,000	18	9.5
	No response	4	2.1

Descriptive Statistics

Child Characteristics

The vast majority of respondents (84.7%) had only one child with an NDD. The average current age of caregivers' children with NDD was 11.6 years. Approximately two thirds of these children were male (63.2%) and one third female (36.8%). See **Tables 6 and 7**.

Table 6. Frequencies for questions related to affected child, family, and caregiving role [*N* = 190]

Variable / Question	Response	*N*	%
Children with NDD	0*	1	.5
(*How many children do you have with some kind of NDD?*)	1	161	84.7
	2	21	11.1
	3	5	2.6
	4	1	.5
	No response	1	.5
Child's gender	Male	120	63.2
(*What is your child's gender?*)	Female	70	36.8
Affected family members	Yes	57	30.0
(*As far as you know, does your child have other members with a known/diagnosed NDD?)*	No	133	70.0
Relationship to child	Biological parent	179	94.2
(*What is your relationship to your child?*)	Adoptive parent	8	4.2
	Other	3	1.6
	Niece	1	.5
	Legal guardian	1	.5
	Child of grandchild's mother from different marriage	1	.5
Length of caregiving relationship	His/her whole life	183	96.3
(*How long have you been in the caregiving role for your child?*)	Most of his/her life	6	3.1
	About half of his/her life	1	0.5
Child's living situation	Yes, all of the time	182	95.8
(*Does your child live at home with you?*)	Yes, part of the time	4	2.1
	No	4	2.1
Care partner	Yes, all of the time	135	71.1
(*Do you have a partner in providing care for your child?*)	Yes, part of the time	31	16.3
	No	24	12.6

* Value was assumed to be erroneous and was omitted from analyses

Note: One respondent answered that they had "11" children with NDD. Based on their responses to other questions, it was assumed that this was a typographical error and that they intended to write "1". Their response to this question was changed accordingly.

Caregiving Roles, Family Structure, and Living Situation

The majority of caregivers reported that their child had no other family members known to have an NDD (70.0%). A total of 94.2% of respondents reported that they were the biological parent of the child in their care. The overwhelming majority of respondents had been in a caregiving role for their child's entire life (96.3%), and shared a home with their child all of the time (95.8%). Most had a partner in caring for their child at least some of the time, with 71.1% of respondents reporting a full-time care partner and 16.3% reporting a part-time partner. See **Table 6** above.

Table 7. Descriptive statistics for all numerical variables

Variable / Question	***N***	***M***	***SD***	**Range**
Caregiver's age (years) (*What is your current age?*)	189	43.80	9.53	27 – 74
Child's age (years) (*How old is your child currently?*)	182	11.65	7.74	1 – 42
Child's age at exome results (years) (*How old was your child when you received results from exome testing?*)	184	8.35	7.51	0 – 42
Child's age at initial concerns (months) (*How old was your child when you first had concerns about their behavior or development?*)	187	13.37	16.93	0 – 144
Child's age at clinical attention (years) (*How old was your child when you sought out a behavioral or medical specialist about your concerns for your child's development?*)	187	1.36	2.00	0 – 15
Children with NDD (*How many children do you have with some kind of NDD?*)	189	1.23	.87	0* – 4
Children with ES for NDD (*How many children do you have who had exome testing for an NDD?*)	189	1.13	.49	1 – 5*
Time since ES (Child's age – age at exome results)	177	3.21	2.47	0 – 17
Time since clinical attention (Child's age – age at clinical attention)	179	10.37	7.54	0 – 40

* Value was assumed to be erroneous and was omitted from analyses

Clinical Characteristics and Timeline

The average child's age at which caregivers sought specialist attention was 1.4 years, while the average child's age at which ES was completed was 8.4 years. On average, at the time of completing the survey, 3.2 years had passed since receiving results from exome sequencing, and 10.4 years had passed since caregivers first sought clinical attention for their child (see **Table 7**). Mirroring the institution breakdown in recruitment, 86.8% of respondents' children had ES testing ordered through Kennedy Krieger Institute and 13.2% through Johns Hopkins Medicine. The majority of respondents (83.7%) shared that they had already received some kind of diagnosis from a provider for their child's neurodevelopmental differences (see **Table 8**).

The most common NDD diagnosis or symptom was developmental delay (87.9%), followed by intellectual disability (62.1%) and autism spectrum disorder (45.3%). Out of the list of 19 skills provided, caregivers most frequently reported that their child needed help with participating in activities at school or in the community (74.7%), telling people what s/he wants (74.2%), and learning new things (71.6%) (see **Tables 10 and 11**).

Respondents were asked to indicate the result of their child's ES. In total, 42.6% of respondents reported a positive/abnormal result, 31.1% reported a VUS/inconclusive result, 22.1% reported a negative/normal result, and 4.2% were not sure. Exactly half of caregivers (50.0%) shared that they felt that they were still seeking an explanation for their child's neurodevelopmental differences (see **Table 8**).

When further categorizing respondents into whether they had received diagnostic (positive) or non-diagnostic (VUS or negative) ES results, we were able to more clearly discern patterns in the data regarding the perceived explanatory power of ES. Among caregivers whose child received diagnostic ES results, the greatest proportion (48.2%) felt that the findings from

ES completely explained their child's differences. None reported that the ES results did *not* explain their child's NDD or only explained it a little. Among caregivers whose child received a non-diagnostic result, over half (57.4%) believed that the ES results did not explain their child's neurodevelopmental differences, with 22.8% reporting "a little" and 14.8% reporting "partly". In both groups, the majority of caregivers were not still seeking an explanation for their child's differences, though this proportion was higher in the group of caregivers whose child had diagnostic ES results (76.5%) compared to children with non-diagnostic ES results (64.4%). See **Table 9**.

Table 8. Frequencies for questions related to diagnosis and clinical genetics experience [*N* = 190]

Variable / Question	**Response**	***N***	**%**
ES results (*What was the outcome of exome testing in your child?*)	Positive (abnormal) Negative (normal) Variant of uncertain significance (VUS) (inconclusive) I'm not sure	81 42 59 8	42.6 22.1 31.1 4.2
ES results as explanation (*How much do you feel the exome findings explain your child's neurodevelopmental differences?*)	Not at all A little Partly Mostly Completely	63 24 30 35 39	33.0 12.6 15.7 18.3 20.4
Seeking explanation (*Do you feel that you are still searching for an explanation for your child's neurodevelopmental differences?*)	Yes No	95 95	50.0 50.0
Institution (*Where did you see the doctor who ordered your child's genetic testing?*)	Kennedy Krieger Institute Johns Hopkins Medicine	165 25	86.8 13.2
Reported NDD diagnosis (*Has a provider given you a diagnosis for your child's neurodevelopmental differences?*)	Yes No I'm not sure	159 27 4	83.7 14.2 2.1
Perceived severity (*From your perspective, how serious is your child's condition compared to other people with an NDD?)*	Much less severe Somewhat less severe No more or less severe Somewhat more severe Much more severe *No response*	22 37 54 58 17 2	11.6 19.5 28.4 30.5 8.9 1.1

Table 9. Frequencies for "ES results as explanation" and "seeking explanation" variables by diagnostic or non-diagnostic ES results [*N* = 182]

Variable / Question	Group	Response	*N*	%
ES results as explanation (*How much do you feel the exome findings explain your child's neurodevelopmental differences?*)	Diagnostic (positive) (*N* = 81)	Not at all	0	0.0
		A little	0	0.0
		Partly	12	14.8
		Mostly	30	37.0
		Completely	39	48.2
	Non-diagnostic (negative or VUS) (*N* = 101)	Not at all	58	57.4
		A little	23	22.8
		Partly	15	14.8
		Mostly	5	5.0
		Completely	0	0.0
Seeking explanation *Do you feel that you are still searching for an explanation for your child's neuro-developmental differences?*)	Diagnostic (positive) (*N* = 81)	Yes	19	23.5
		No	62	76.5
	Non-diagnostic (negative or VUS) (*N* = 101)	Yes	36	35.6
		No	65	64.4

Note: The eight respondents who answered "I don't know" for ES results are excluded from this table.

Question: Please check the boxes that describe problems that your child experiences. Check as many as apply to your child.

Table 10. Descriptive statistics and frequencies for child's symptoms/diagnoses [*N* = 190]

	Frequency (*N* = 190)		**Count (*N* = 8)**		
NDD Symptom/Diagnosis	***N***	**%**	***M***	***SD***	**Range**
Developmental delay	167	87.9	3.21	1.34	1 – 7
Intellectual disability	118	62.1			
Autism / autism spectrum disorder	86	45.3			
Other neurological problem*	70	36.8			
Epilepsy / seizures	66	34.7			
Movement disorder	58	30.5			
Cerebral palsy	32	16.8			
Birth defects	13	6.8			

* For "other neurological problem," a space was provided for respondents to elaborate. Answers included "ataxia," "Floating Harbor Syndrome," "cerebral artery occlusion," "dystonia," "abnormal ocular movements," "tremors," "leukodystrophy," "dysautonomia," among others.

Question: Please check the boxes below the describe tasks or skills that your child needs help with. Check as many apply to your child.

Table 11. Descriptive statistics and frequencies for child's difficulties [*N* = 190]

	Frequency (*N* = 190)		**Count (*N* = 17)**		
Task/Skill	***N***	**%**	***M***	***SD***	**Range**
Participating in activities at school or in the community	142	74.7	8.68	4.41	0 – 17
Telling people what s/he wants	141	74.2			
Learning new things	136	71.6			
Dressing or undressing self	115	60.5			
Behaving in an appropriate manner	113	59.5			
Toileting	110	57.9			
Participating in activities at home	109	57.4			
Understanding other people	103	54.2			
Regulating his/her mood	94	49.5			
Moving around at home, school, and/or community	92	48.4			
Remembering things s/he knows	90	47.4			
Using his/her hands and arms to do the things s/he wants to do	82	43.2			
Sleeping each night	81	42.6			
Performing functions such as feeding/eating	73	38.4			
Getting along with children	59	31.1			
Getting along with adults	43	22.6			
Managing his/her pain	36	18.9			
Seeing	25	13.2			
Hearing	7	3.7			

Impact of COVID-19

The majority of respondents (63.9%) had been under a shelter-in-place or stay-at-home order at some point since the beginning of the COVID-19 pandemic in the United States in March 2020. However, over half (58.1%) stated that they were no longer under these restrictions at the time of their response to the survey. The majority of participants (58.6%) stated that they spent much more time caring for their child now than before COVID-19. Most participants experienced interruptions to their child's therapies and services, with 49.7% reporting that *all* were disrupted and 35.6% reporting that *some* were disrupted. The greatest proportion of respondents (45.0%) shared that they did not experience financial difficulties as a result of the pandemic, with an additional 39.8% noting non-serious or minor financial strain. See **Tables 12 and 13** below.

Table 12. Frequencies for questions related to impact of COVID-19 [*N* = 190]

Variable / Question	Response	*N*	%
Shelter-in-place order (*At any point since March, have you been living under a shelter-in-place or shelter-at-home order?*)	Yes	121	63.7
	No	66	34.7
	No response	3	1.6
Shelter-in-place status (*Are you still under the shelter-in-place order?*)	Yes	11	5.8
	No	110	57.9
	No response	69	36.3
COVID caregiving (*In thinking about the time before COVID-19 compared to now, how has your caregiving situation changed?*)	Much more time caring for my child	111	58.4
	A little more time caring for my child	30	15.8
	Same amount of time caring for my child	41	21.6
	A little less time caring for my child	4	2.1
	Much less time caring for my child	4	2.1
COVID services (*Have you had any interruption of therapies or other services for your child due to COVID-19?*)	Yes, all interrupted	94	49.5
	Yes, some interrupted	68	35.8
	No, none interrupted	17	8.9
	No response	11	5.8
COVID financial difficulties (*Have you had financial difficulties due to COVID-19?*)	Yes, serious	17	8.9
	Yes, some that I don't consider serious	37	19.5
	Yes, minor	38	20.0
	No	86	45.3
	I don't know yet	4	2.1
	I prefer not to answer	7	3.7
	No response	1	.5

Table 13. Descriptive statistics for questions related to impact of COVID-19 [*N* = 190]

Variable / Question	*N*	*M*	*SD*	Range
Shelter-in-place duration (present) (*For how many months have you been sheltering in place?*)	11	6.45	.82	5 – 8
Shelter-in-place duration (past) (*For how many months were you sheltering in place?*)	101	3.08	1.44	0 – 8

Factor Analyses: PAS, PUCHS, and COVID-19 Impact Questions

Because the PAS and the PUCHS are relatively new validated scales that have each been utilized in fewer than five published studies, a factor analysis was conducted for each. A factor analysis was also run on the three novel questions created for this study concerning the impact of the COVID-19 pandemic on caregiving, child's services, and finances. The factor analysis procedure described below was adapted from Field (2013) and from Laerd Statistics (2017c).

Psychological Adaptation Scale (PAS)

To start, the factorability of the 20 PAS items was examined using several established criteria. All 20 items correlated with at least one other item at $r \geq .3$, suggesting reasonable factorability (Laerd Statistics 2017c). The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was .935, which is considered "marvelous" according to Kaiser's (1974) classification of measure values. Bartlett's test of sphericity was significant ($\chi^2(190) = 2812.14$, $p < .05$). Lastly, the communalities were all above .3, helping to confirm that each item shared some common variance with other items. Given these overall indicators, we determined that factor analysis would be suitable for this scale.

Principal axis factoring (PAF) was run on the PAS per the suggestion of Field (2013), with extraction initially based on eigenvalues greater than 1. We utilized direct oblimin, an oblique rotation, in which factors are allowed to correlate. Small coefficients with an absolute value below .3 were suppressed to facilitate pattern discernment. PAF revealed three components with eigenvalues greater than 1, which explained a cumulative 66.8% of the total variance. Visual inspection of the scree plot suggested that retaining four components would be appropriate. This coheres with the four-factor model suggested by Biesecker and colleagues' (2013) confirmatory factor analysis.

The analysis was rerun, this time fixing extraction at four factors. The four-component solution explained 71.3% of the total variance, met the interpretability criterion, and displayed overall 'simple structure' (Laerd Statistics 2017). The interpretation of the data was consistent with the dimensions of adaptation that the PAS is designed to measure, with four coping efficacy items loading on Domain 1, four self-esteem items on Domain 2, four social integration items on Domain 3, and four spiritual wellbeing items on Domain 4. A table displaying factor loadings is provided in **Appendix F.**

Parental Uncertainty About a Child's Health Scale (PUCHS)

The factorability of the 15 weighted PUCHS items was examined using several established criteria. Weighted items were calculated by multiplying the unweighted item from Part A by its corresponding weight from Part B. All items correlated with at least one other item at $r \geq .3$, suggesting reasonable factorability (Laerd Statistics 2017c). The KMO measure of sampling adequacy was .857, which is considered "meritorious" according to Kaiser's (1974) classification of measure values. Bartlett's test of sphericity was significant ($\chi^2(105) = 1632.49$, $p < .05$). All communalities were all above .3 except for item 4 (.035), helping to confirm that most items shared some common variance with other items. Given these overall indicators, we determined that factor analysis would be suitable for this scale.

Principal axis factoring (PAF) was run on the PUCHS fixing extraction at four factors. We selected this number of factors based on the four-factor models derived in the three previous studies that used the PUCHS (Macnamara 2014; Yanes et al. 2017; Bell et al. 2019). We utilized direct oblimin, an oblique rotation, in which factors are allowed to correlate. The four-component solution explained 67.6% of the total variance, met the interpretability criterion, and displayed overall 'simple structure' (Laerd Statistics 2017c).

In our factor analysis, Domain 1 consisted of items 1, 2, 5, and 6; Domain 2 consisted of items 7, 8, 9, 10, and 11; Domain 3 consisted of items 3, 12, and 13; and Domain 4 consisted of items 14 and 15. A table displaying factor loadings is provided in **Appendix F**. Item 4 did not load on any of the four factors and thus was removed from the scale. The same item was excluded during model refinement by Umstead and colleagues (n.d.). In addition, item 3 ("unsure of whether my child is expected to have a normal lifespan") loaded on Domain 3, but its coefficient was relatively small (.32) and it conceptually diverged from the other two items in its domain. Due to this incongruity, item 3 was also removed from the scale, leaving a total of 13 weighted items (26 total questions) loading on four domains. Scoring was adjusted to account for the exclusion of these two items. Domain labels were adopted from previous publications and modified to reflect the items that loaded on them. The final four subscales were Medical Management (four weighted items), Family/Reproductive (five weighted items), Social (two weighted items), and Existential (two weighted items).

COVID-19 Impact Questions

To determine whether the three COVID-19 questions hung together and could be reduced to a single score or component, the same procedure was run as that described for the PAS and PUCHS above. The applied factorability criteria suggested poor factorability for these items. Correlation coefficients fell well below the established threshold of $r \geq .3$. The KMO measure of sampling adequacy was .554, which is considered "miserable" according to Kaiser's (1974) classification of measure values. Finally, the one component with an eigenvalue greater than 1 explained only 42.5% of the total variance. Given these indicators, no further factor analysis was performed, and the three questions were treated as separate, individual items in subsequent analyses.

Summary Statistics for Key Dependent and Independent Variables

Means, standard deviations, medians, and ranges for each scale and subscale are presented in **Table 14.** The following data in parentheses are presented as mean ± standard deviation. Most participants endorsed beliefs about the chronic nature of their child's condition (chronicity: 26.93 ± 3.54) and perceived it as having a significant impact (consequences: 23.66 ± 4.34). Participants felt that they had a moderate degree of personal control over their child's condition (personal control: 19.92 ± 5.02), but fairly low treatment control (treatment control: 14.30 ± 4.00). Participants reported that they found it moderately difficult to make sense of their child's condition (coherence: 16.88 ± 4.98). In general, participants did not strongly believe that their child's condition followed a cyclical pattern (cyclicity: 10.40 ± 4.19). Participants felt that their child's NDD modestly affected them emotionally (emotional representation: 19.72 ± 4.59).

Participants held a moderately strong agreement that genetics was a cause for their child's NDD (genetics/heredity causal attribution: 4.03 ± 1.16). When asked to "list in rank-order the three most important factors you now believe caused your child's condition," the majority of participants who responded (62.6%) indicated "genetics" or some variant thereof as the most important factor in causing their child's NDD. Other causal factors ranked first included God's will (8.4%), chance or luck (5.6%), and pregnancy complication or concern (3.9%).

Participants' weighted uncertainty was moderately low (PUCHS: 1.59 ± .88). Within dimensions of uncertainty, uncertainty related to medical management for their child's NDD (1.61 ± .98), to family and reproductive issues (1.62 ± 1.05), and to social support (2.03 ± 1.33) was also moderately low. Respondents indicated low levels of uncertainty related to the meaning of the child's life (1.00 ± 1.12).

Overall, participants in this study were moderately well-adapted to their child's neurodevelopmental disorder (PAS: 3.75 ± 0.74). Specifically, participants showed moderately high levels of coping efficacy (3.89 ± 0.88), self-esteem (3.88 ± 0.83), and social integration (3.84 ± 0.88). Participants indicated moderate levels of spiritual wellbeing (3.39 ± 1.01). Respondents' levels of depression, anxiety, and stress were low on the whole (DASS-21: 7.39 ± 9.21; 4.49 ± 6.37; 13.7 ± 10.18, respectively).

Table 14. Summary statistics for key independent and dependent scale variables [$N = 190$]

Variable (Scale), Number of Items	*M*	Median	*SD*	Study sample range	Possible range
Total weighted uncertainty (PUCHS), 13 weighted items	1.59	1.51	.88	0 – 4	0 – 4
Medical management uncertainty (PUCHS), 4 weighted items	1.61	1.54	.98	0 – 4	0 – 4
Family/reproductive uncertainty (PUCHS), 5 weighted items	1.52	1.30	1.05	0 – 4	0 – 4
Social uncertainty (PUCHS), 2 weighted items	2.03	2.00	1.33	0 – 4	0 – 4
Existential uncertainty (PUCHS), 2 weighted items	1.00	1.00	1.12	0 – 4	0 – 4
Chronicity (IPQ-RA), 6 items	26.93	28.00	3.48	12 – 30	6 – 30
Consequences (IPQ-RA), 6 items	23.58	24.00	4.34	11 – 30	6 – 30
Personal control (IPQ-RA), 5 items	19.92	21.00	5.02	6 – 30	5 – 25
Treatment control (IPQ-RA), 5 items	14.30	15.00	4.00	5 – 25	5 – 25
Coherence (IPQ-RA), 5 items	16.75	17.00	4.98	5 – 25	5 – 25
Cyclicity (IPQ-RA), 4 items	10.40	10.00	4.19	4 – 20	4 – 20
Emotional representation (IPQ-RA), 6 items	19.72	20.00	4.59	6 – 30	6 – 30
Genetic causal attribution (IPQ-RA), 1 item	4.03	4.00	1.16	1 – 5	1 – 5
Psychological adaptation (PAS), 20 items	3.75	3.80	0.74	1 – 5	1 – 5
Coping efficacy (PAS), 5 items	3.89	4.00	0.79	1 – 5	1 – 5
Self-esteem (PAS), 5 items	3.88	4.00	0.83	1 – 5	1 – 5
Social integration (PAS), 5 items	3.84	4.00	0.77	1 – 5	1 – 5
Spiritual wellbeing (PAS), 5 items	3.39	3.40	1.01	1 – 5	1 – 5
Depression (DASS-21), 7 items	7.39	4.00	9.21	0 – 38	0 – 42
Anxiety (DASS-21), 7 items	4.49	2.00	6.37	0 – 34	0 – 42
Stress (DASS-21), 7 items	13.73	12.00	10.18	0 – 42	0 – 42

Internal Reliability of Scales

All scales demonstrated good to excellent internal reliability as determined by $\alpha > 0.70$ (Cronbach 1951). The IPQ-RA had an $\alpha = 0.72$, the PUCHS (13 weighted items) had an $\alpha = 0.90$, the PAS had an $\alpha = 0.95$, and the DASS-21 had an $\alpha = 0.94$. For the PUCHS subscales, Medical Management had an $\alpha = 0.79$, Family/Reproductive had an $\alpha = 0.86$, Social had an $\alpha = 0.94$, and Existential had an $\alpha = 0.91$.

Test for Display Order Effects

The display order of the PAS and PUCHS in the survey was randomized for respondents. Independent samples t-tests were conducted for the total PAS score, total PUCHS score, and for the 26 individual questions on the PUCHS to investigate the presence of order effects. Two questions on the PUCHS (2a and 13b) were found to differ significantly ($p \leq .05$) based on viewing the PAS or the PUCHS first. However, there was no significant difference in overall raw PAS or PUCHS scores between the two display order groups. Because there were individual items that varied significantly on the basis of display order, display order was included in logistic regression models. See **Table 15** below.

Table 15. T-test for order effects of PAS display order [$N = 190$]

	Order PAS Displayed 1st, PUCHS 2nd ($N = 92$)		Order PAS Displayed 2nd, PUCHS 1st ($N = 98$)		95% CI for Mean Difference	t	p
	M	*SD*	*M*	*SD*			
PUCHS Q2a*	2.09	1.24	1.65	1.24	.08, .79	**2.41**	**.02**
PUCHS Q13b*	3.84	1.16	4.15	1.01	-.63, -.01	**-2.01**	**.05**
PUCHS Total (13 weighted)	1.70	.80	1.49	.94	-.06, .45	1.54	.13
PAS Mean	3.80	.71	3.71	.76	-.13, .29	.72	.44

Note: Bolded values represent statistically significant differences at $p \leq .05$.
* Range of scores for questions on Part A of the PUCHS is 0 to 4. Range of scores for questions on Part B of the PUCHS is 1 to 5.

A Priori Hypothesis Testing

For the purposes of the following analyses, participants who responded "I don't know" to the question about ES results ($N = 8$) were excluded, leaving a sample size of $N = 182$. Prior to construction of full logistic regression models, univariate analyses were run between all key/predictor (independent) variables and the outcome (dependent) variable of interest to determine which predictors would be included in the corresponding models. Relationships significant at $p \leq .30$ were included in regression analyses. These values are reported in **Table 16**.

Table 16. Betas and *p*-values for univariate logistic regressions of dichotomized outcome variables (top row) on independent variables (left column) [*N* = 182]

Variable[†]	**Adaptation** ***B* (*p*)**	**Depression** ***B* (*p*)**	**Anxiety** ***B* (*p*)**	**Stress** ***B* (*p*)**
Control variables				
Children with NDD	**-.44 (.14)**	**.43 (.11)**	**.53 (.07)**	-.02 (.93)
Child's age	.01 (.77)	.01 (.76)	.01 (.66)	.00 (.83)
Caregiver's age	**-.02 (.28)**	.01 (.53)	.00 (.85)	.01 (.42)
Caregiver's education	**-.16 (.24)**	-.08 (.56)	-.03 (.88)	.13 (.34)
Caregiver's income	-.03 (.81)	**-.19 (.13)**	.05 (.71)	-.03 (.78)
Caregiver's gender	.02 (.96)	-.02 (.97)	.24 (.69)	.01 (.99)
PAS/PUCHS display order	.10 (.73)	**-1.39 (<.01)**	**-.49 (.16)**	**-.49 (.11)**
COVID caregiving	.08 (.56)	.04 (.80)	**-.21 (.20)**	.10 (.50)
COVID therapies	**-.24 (.30)**	**.36 (.18)**	.13 (.65)	**.55 (.03)**
COVID financial	-.14 (.35)	**.42 (<.01)**	**.18 (.29)**	**.45 (<.01)**
Child symptoms/diagnoses	-.10 (.35)	**.18 (.14)**	**.20 (.13)**	**.12 (.30)**
Child difficulties	-.02 (.53)	**.09 (.02)**	**.10 (.03)**	**.11 (<.01)**
Perceived seriousness	.00 (.98)	**.04 (.03)**	**.30 (.06)**	**.28 (.04)**
Explanatory power	-.06 (.55)	**-.23 (.04)**	**-.26 (.03)**	**-.15 (.13)**
Key variables				
Chronicity	-.03 (.48)	**.07 (.20)**	**.19 (.01)**	**.05 (.27)**
Consequences	**-.04 (.19)**	**.09 (.02)**	**.12 (.01)**	**.12 (<.01)**
Personal control	**.05 (.10)**	**-.09 (<.01)**	**-.06 (.09)**	**-.03 (.28)**
Treatment control	**.05 (.17)**	**-.04 (.28)**	-.04 (.32)	-.02 (.58)
Coherence	.02 (.46)	-.02 (.60)	**-.07 (.04)**	**-.05 (.14)**
Cyclicity	.01 (.80)	.02 (.59)	.02 (.57)	.04 (.31)
Emotional representation	**-.08 (.01)**	**.19 (<.01)**	**.19 (<.01)**	**.22 (<.01)**
Genetic causal attribution	-.10 (.44)	-.05 (.71)	-.07 (.62)	**-.15 (.23)**
Time since ES	.02 (.69)	-.01 (.87)	-.04 (.61)	.04 (.58)
Time since clinical attention	.00 (.85)	.00 (.99)	.01 (.85)	.01 (.75)
ES results: VUS vs. positive	-.04 (.88)	**-.56 (.10)**	**-.54 (.14)**	-.28 (.36)
ES results: VUS vs. neg	**-.40 (.21)**	.15 (.67)	.25 (.50)	**.46 (.15)**
Uncertainty (total)	-.16 (.35)	**.60 (<.01)**	**.56 (<.01)**	**.51 (<.01)**
Medical management	-.12 (.44)			
Family/reproductive	.03 (.85)			
Social	**-.18 (.16)**			
Existential	**-.25 (.06)**			

Note: Outcome variables were dichotomized in the following ways: *Adaptation*: split at the mean (3.75); *Depression, Anxiety, Stress*: split at value delineating "normal" from "abnormal" per DASS-21 scoring guide (Lovibond & Lovibond 1995), cut-points are 9, 7, and 14, respectively

[†] Relationships that are statistically significant at $p \leq .30$ are bolded in the corresponding cell of the table. Note that all control variables ("children with NDD" through "explanatory power") were included in subsequent regression models regardless of statistical significance.

<u>Aim 1</u>: Influence of ES Results Category on NDD Appraisals

Hypothesis 1.1.

A series of one-way ANOVA were conducted to determine if illness appraisals (scores on each IPQ-RA subscale, genetic causal attribution, and uncertainty via the PUCHS) were different for caregivers whose children received different types of ES results. Two of the eight analyzed illness representation dimensions, as well as uncertainty, revealed significant differences between groups with different kinds of test results. The one-way ANOVA analyses are summarized in **Table 17(a)**, with results of post-hoc contrasts for the three statistically significant ANOVA summarized in **Table 17(b)**.

Treatment control perceptions differed between categories of ES results, $F(2,180) = 3.90$, $p < .05$. Treatment control score increased from the positive ES (13.36 ± 3.82), to VUS (14.86 ± 3.90), to negative ES (15.02 ± 3.84) results groups, in that order, indicating that caregivers who reported negative ES results held the strongest beliefs about the controllability of their child's NDD through treatment. Tukey-Kramer post-hoc analysis revealed that a statistically significant difference between the positive and negative results groups (1.66, 95% CI (0.10 to 3.21), $p < .05$), but no other group differences were statistically significant.

Coherence was statistically significantly different between categories of ES results, $F(2,180) = 10.14$, $p < .01$. Coherence score increased from the VUS (15.21 ± 5.18), to negative ES (15.75 ± 5.07), to positive ES (18.65 ± 4.14) results groups, in that order, indicating that caregivers who reported positive ES results felt most strongly that their child's NDD made sense. Games-Howell (for unequal variances) post-hoc analysis revealed a statistically significant difference between the VUS and positive results groups (3.44, 95% CI (1.34 to 5.54), $p < .01$) ,

as well as a statistically significant difference between the negative and positive groups (2.90, 95% CI (.99 to 4.81), $p < .01$).

Weighted uncertainty as measured by the PUCHS was statistically significantly different across the categories of ES results, $F(2,180) = 8.32$, $p < .01$. Uncertainty score increased from the positive (1.32 ± .85), to negative (1.76 ± .85), to VUS (1.92 ± .87) ES results groups, in that order, indicating that caregivers who reported a VUS result had the highest levels of uncertainty. Tukey-Kramer post-hoc analysis revealed a statistically significant difference between the VUS and positive ES results groups (.60, 95% CI (.22 to .99), $p < .01$), and a statistically significant difference between the negative and positive ES results groups (.44, 95% CI (.09 to .79), $p = .01$).

No significant intergroup differences were found for the chronicity, consequences, personal control, cyclicity, emotional representation, or genetic causal attribution dimensions of the IPQ-RA.

Table 17(a): One-way ANOVA of illness representations and uncertainty by ES results group [*N* = 182]

	ES Results Group							
	Positive (*N* = 81)		Negative (*N* = 59)		VUS (*N* = 42)			
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*
Chronicity	27.51	3.28	26.86	2.86	26.63	3.40	1.30	.28
Consequences	23.59	4.02	23.53	4.74	23.14	4.42	.16	.85
Personal control	19.36	5.34	20.15	4.54	20.42	4.97	.78	.46
Treatment control	13.36	3.82	15.02	3.84	14.86	3.90	**3.90**	**.02**
Coherence	18.65	4.14	15.75	5.07	15.21	5.18	**10.14**	**< .01**
Cyclicity	9.75	4.07	11.44	4.32	10.60	3.91	2.89	.06
Emotional representation	19.42	4.89	19.95	4.29	19.64	4.58	.32	.73
Genetic causal attribution	4.15	1.26	4.00	1.10	3.95	.98	.51	.60
Uncertainty	1.32	.85	1.76	.85	1.92	.87	8.32	**< .01**

Note: Bolded values represent statistically significant contrasts at $p < .05$.

Table 17(b): Tukey-Kramer and Games-Howell post-hoc tests for pairwise comparisons of significant illness representations and uncertainty by ES results group [*N* = 182]

Outcome Variable	**Contrast**	**Mean Difference**	***p***	**95% Confidence Interval**	
				Lower	**Upper**
Treatment control *(Tukey-Kramer)*	VUS vs. positive	1.50	.10	-.21	3.22
	VUS vs. negative	.16	.98	-1.66	.20
	Positive vs. negative	**1.66**	**.03**	.10	3.21
Coherence *(Games-Howell)*	VUS vs. positive	**3.44**	**<.01**	1.25	5.63
	VUS vs. negative	.54	.86	-1.92	2.99
	Positive vs. negative	**2.90**	**<.01**	.99	4.81
Uncertainty *(Tukey-Kramer)*	VUS vs. positive	**.60**	**<.01**	.22	.99
	VUS vs. negative	.16	.62	-.25	.57
	Positive vs. negative	**.44**	**.01**	.09	.79

Note: Bolded values represent statistically significant contrasts at $p < .05$.

Hypothesis 1.2.

To test the moderating effects of uncertainty, a median split was applied to the weighted uncertainty variable (PUCHS score) with a cut-point at 1.51. This cut-point was generated by running the visual binning operation in SPSS and dividing the data into two equal centiles, as no guidance is provided in the literature on how to convert the PUCHS score to a dichotomous categorical variable. Any values up to and including 1.51 were categorized as 1 = "low uncertainty," and values above 1.51 were categorized as 2 = "high uncertainty." Any significant interactions between the dichotomous uncertainty variable and ES results type would indicate moderation.

A series of two-way ANOVA were conducted to examine the effects of ES results category and uncertainty level on illness representations. Residual analysis was performed to test for the assumptions of the two-way ANOVA. Outliers were assessed by inspection of a box-plot and homogeneity of variances was assessed by Levene's test. There were no outliers, and the assumption of homogeneity of variances was violated, as assessed by Levene's test for equality of variances, $p = .005$ for coherence.

None of the interaction effects between ES results category and uncertainty on illness representation dimensions were statistically significant (see **Table 18**). For treatment control and coherence, statistically significant main effects were found for ES results, mirroring the findings discussed above under Hypothesis 1.1. There were significant main effects found for uncertainty on personal control, $F(1,177) = 4.57$, $p < .05$, on coherence, $F(1,177) = 12.76$, $p < .01$, and on emotional representation, $F(1,177) = 4.07$, $p = .05$. Greater perceived uncertainty was associated with lower perceived personal control, lower perceived coherence, and greater degree of negative emotional representation (stronger unfavorable feelings) of the child's NDD.

Table 18. Main effects and interactions from 2 x 3 two-way ANOVA of illness representations (uncertainty by ES results category) [$N = 182$]

IPQ-RA Subscale	Main Effects and Interaction	df	*F*	*p*	Equality of Variances (Levene)
Chronicity	Uncertainty	1	.00	.99	Passed
	ES Results	2	1.03	.36	($p = .51$)
	Interaction	2	.67	.51	
	Corrected model	5	.80	.55	
Consequences	Uncertainty	1	.00	.97	Passed
	ES Results	2	.17	.87	($p = .13$)
	Interaction	2	1.93	.17	
	Corrected model	5	.88	.50	
Personal control	Uncertainty	1	**4.57**	**.03**	Passed
	ES Results	2	1.51	.22	($p = .06$)
	Interaction	2	.55	.58	
	Corrected model	5	1.43	.21	
Treatment control	Uncertainty	1	.62	.43	Passed
	ES Results	2	**3.96**	**.02**	($p = .78$)
	Interaction	2	.70	.50	
	Corrected model	5	1.94	.09	
Coherence	Uncertainty	1	**12.76**	**<.01**	Violated
	ES Results	2	**5.19**	**<.01**	($p = .01$)
	Interaction	2	2.83	.06	
	Corrected model	5	**8.14**	**<.01**	
Cyclicity	Uncertainty	1	1.41	.24	Passed
	ES Results	2	1.75	.18	($p = .30$)
	Interaction	2	.17	.84	
	Corrected model	5	1.60	.16	
Emotional representation	Uncertainty	1	**4.07**	**.05**	Passed
	ES Results	2	.03	.97	($p = .81$)
	Interaction	2	1.24	.29	
	Corrected model	5	1.83	.11	
Genetic causal attribution	Uncertainty	1	.13	.72	Violated
	ES Results	2	.32	.73	($p = .03$)
	Interaction	2	1.28	.28	
	Corrected model	5	.83	.53	

Note: Bolded values represent statistically significant contrasts at $p \leq .05$.

Aim 2: NDD Appraisals as Predictors of Adaptation and Affective Outcomes

Hypothesis 2.1.

Univariate linear regressions were conducted between each predictor variable and the outcome variables (psychological adaptation, depression, anxiety, and stress). However, residual plots indicated a lack of linearity between all pairs of variables, violating an integral assumption of linear regression analysis (for scatterplot visualizations, see **Appendix G**). As such, binomial logistic regression analyses were conducted to assess the ability of the independent variables to predict high or low levels of the four outcomes.

To dichotomize psychological adaptation, a mean split was conducted wherein values up to and including the mean from the PAS (3.75) were categorized as 0/"low" and values greater than 3.75 were categorized as 1/"high". For the affective outcome variables, cut-points for dichotomization were established by the DASS-21 scoring guide (Lovibond & Lovibond 1995). Depression scores greater than 9, Anxiety scores greater than 7, and Stress scores greater than 14 were considered beyond the "normal" range. See **Appendix B** for a summary of the variable dichotomization scheme.

To determine which key variables would be included in each logistic regression model, a series of univariate logistic regression analyses were first conducted regressing each of the four dichotomous outcome variables. Any relationships that displayed significance at $p \leq .30$ were included in the corresponding hierarchical logistic regression models (refer to **Table 19**).

Psychological adaptation. A hierarchical binomial logistic regression was performed to ascertain the effects of four illness representation dimensions (consequences, personal control, treatment control, and emotional representation), the VUS-versus-negative ES results comparison, and two uncertainty dimensions (social and existential) on the likelihood that

participants are better adapted to their child's NDD ($N = 96$). Linearity of the continuous variables with respect to the logit (log odds transformation) of the dependent variable was assessed via the Box-Tidwell (1962) procedure. As part of this procedure, all continuous predictor variables were transformed into their natural logs (ln(variable)). Then, interaction terms between the predictor variable and its natural log were created (variable * ln(variable)) and entered into the regression model along with the untransformed predictor variables. Per the Box-Tidwell guidance, if these interaction terms *fail* to reach statistical significance, then the assumption of linearity is upheld (Laerd Statistics 2017b).

In addition, a Bonferroni correction was applied using all 21 terms in the model, resulting in statistical significance for the linearity assumption testing being accepted when $p \leq .002$, obtained by dividing the significance threshold of $p = .05$ by 21 (Tabachnick & Fidell 2014; Laerd Statistics 2017b). Based on this assessment, all continuous independent variables were found to be linearly related to the logit of the dependent variable based on p values greater than .002. Importantly, this adjusted significance level of $p \leq .002$ from the Bonferroni correction was used to determine the statistical significance of individual coefficients in the logistic regression model. Applying Bonferroni correction to regression analysis is advised by numerous statisticians to protect against possible inflation of type I error and bias from repeated testing effects (e.g., Mundfrom et al. 2006; Taylor 2011).

The 14 control variables were entered into the regression model in Step 1, followed by the seven key predictor variables in Step 2. The final logistic regression model reached statistical significance, $\chi^2(22) = 36.31$, $p = .028$. The model correctly classified 72.7% of cases. Sensitivity was 74.4%, specificity was 70.6%, positive predictive value was 75.3%, and negative predictive

value was 69.6%.(see **Table 19**). The overall fit of the model improved by 15.0% (Nagelkerke R^2 9.4% to 24.4%) from Step 1 to Step 2 by adding the set of eight predictor variables.

Of the 22 independent variables, none reached statistical significance based on the Bonferroni adjusted *p* value of .002. However, three of the variables (personal control, emotional representation, and VUS-vs.-negative ES results comparison) displayed trends (see **Table 19**). Caregivers whose child had a VUS ES result had 2.74 times higher odds to report better overall adaptation than caregivers whose child had a negative ES result, when holding other covariates at a fixed value. While holding other covariates at a constant value, increasing perception of personal control over the child's NDD by one point was associated with 14% higher likelihood of being in the group with above-average adaptation. In addition, a one-point increase in negative emotion representation of the child's NDD was associated with an 11% reduction in the likelihood of being in the group with above-average adaptation.

The area under the ROC curve for the regression with adaptation as the dependent variable was .77 (95% CI, .68 to .83), which is an indicator that the model provides an acceptable level of discrimination according to Hosmer et al. (2013). See **Appendix H** for corresponding ROC curve graph.

Table 19. Binomial logistic regression of psychological adaptation on independent variables [$N = 182$]

Step and variable Dependent: Adaptation	*B*	*SE*	Wald χ^2	*p*	Odds Ratio (e^B)	95% CI for Odds Ratio	
						Lower	Upper
(1) Control variables							
Children with NDD	-.34	.30	1.26	.26	.72	.40	1.28
Child's age	.05	.04	1.48	.22	1.05	.97	1.15
Caregiver's age	-.03	.03	.66	.42	.97	.91	1.04
Caregiver's education level	-.30	.18	2.70	.10	.74	.52	1.06
Caregiver's annual income	-.08	.16	.22	.64	.93	.68	1.27
Caregiver's gender	-.46	.64	.51	.47	.63	.18	2.23
PAS/PUCHS display order	.01	.36	.00	.98	1.01	.50	2.02
COVID caregiving	.07	.19	.12	.74	1.07	.73	1.56
COVID therapies	.05	.30	.03	.86	1.05	.59	1.88
COVID financial	-.18	.19	.91	.34	.84	.58	1.21
Child symptoms/diagnoses	-.21	.17	1.57	.21	.81	.58	1.13
Child difficulties	.05	.06	.72	.40	1.05	.94	1.17
Perceived seriousness	-.08	.21	.17	.68	.92	.62	1.37
Explanatory power	.07	.11	.33	.56	1.07	.85	1.34
Constant	3.60	1.68	4.60	.03	36.69		
(2) Control + Key variables							
Children with NDD	-.27	.38	.51	.47	.76	.36	1.60
Child's age	.07	.05	2.19	.14	1.07	.98	1.17
Caregiver's age	-.04	.04	1.16	.28	.96	.89	1.03
Caregiver's education level	-.42	.21	4.17	**.04**	.66	44	.98
Caregiver's annual income	.05	1.8	.09	.76	1.06	.75	1.49
Caregiver's gender	-.97	.74	1.71	.19	.38	.09	.162
PAS/PUCHS display order	-.20	.39	.27	.61	.82	.38	1.76
COVID caregiving	.14	.22	.42	.52	1.15	.75	1.75
COVID therapies	.33	.33	1.03	.31	1.39	.74	2.63
COVID financial	-.18	.21	.76	.38	.83	.55	1.26
Child symptoms/diagnoses	-.19	.19	1.01	.32	.83	.57	1.20
Child difficulties	.07	.07	1.10	.29	1.07	.94	1.22
Perceived seriousness	.04	.23	.03	.87	.104	.66	1.64
Explanatory power	-.18	.14	1.49	.22	.84	.63	1.11
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Consequences	.02	.07	.05	.82	1.02	.89	1.17
Personal control	.13	.06	5.10	**.02**	1.14	1.02	1.27
Treatment control	-.03	.07	.19	.66	.97	.85	1.11
Emotional representation	-.12	.05	5.23	**.02**	.89	.80	.98
ES results: VUS vs. neg	-.98	.43	5.07	**.02**	.38	.16	.88
Social uncertainty	-.23	.16	2.08	.15	.79	.58	1.09
Existential uncertainty	.07	.20	.15	.70	1.08	.74	1.58
Constant	4.03	2.50	2.59	.11	56.12		

Note: Cox & Snell $R^2 = .18$. Nagelkerke $R^2 = .24$. Hosmer & Lemeshow goodness-of-fit test: $\chi^2(8) = 4.86$, $p = .77$.

Bolded values signify coefficients with $p \leq .05$ considered to be trends in the data, which are discussed in more detail in the text.

Depression. A hierarchical binomial logistic regression was performed to ascertain the effects of five illness representation dimensions (chronicity, consequences, personal control, treatment control, and emotional representation), the VUS-versus-positive ES results comparison, and total weighted uncertainty on the likelihood that participants have mild to severe signs of depression ($N = 52$). Linearity of the continuous variables with respect to the logit (log odds transformation) of the dependent variable was assessed via the Box-Tidwell (1962) procedure. Please refer to the preceding section ("Adaptation") for a description of this procedure and its parameters.

As with the logistic regression with adaptation as the dependent variable, a Bonferroni correction was applied using all 22 terms in the model, resulting in statistical significance for the linearity assumption testing being accepted when $p \leq .002$, obtained by dividing the significance threshold of $p = .05$ by 22 (Tabachnick & Fidell 2014; Laerd Statistics 2017b). Based on this assessment, all continuous independent variables were found to be linearly related to the logit of the dependent variable based on p values greater than .002. As before, this adjusted significance level of $p \leq .002$ from the Bonferroni correction was used to determine the statistical significance of individual coefficients in the logistic regression model.

The 14 control variables were entered into the regression model in Step 1, followed by the seven key predictor variables in Step 2. The final logistic regression model reached statistical significance, $\chi^2(21) = 58.19$, $p < .01$. The model correctly classified 81.3% of cases. Sensitivity was 57.5%, specificity was 90.4%, positive predictive value was 69.7%, and negative predictive value was 84.7%. Of the 21 independent variables, two emerged as statistically significant: PAS/PUCHS display order and emotional representation (see **Table 20**). The overall fit power of

the model improved by 17.8% variance explained (Nagelkerke R^2 31.4% to 49.2%) from Step 1 to Step 2 by adding the set of seven predictor variables.

The PAS/PUCHS display order variable was included in the model as a control, but proved statistically significant even once the key variables had been entered. Participants who viewed the PUCHS first and the PAS second (directly before the DASS-21 affective measures) had an 83% lower likelihood of being in the group reporting mild to high depressive symptoms than participants who viewed the PAS second, suggesting a substantial recency or framing effect. Furthermore, holding other covariates at a constant value, a one-point increase on the emotional representation scale was associated with a 39% increase in the odds of being in the mild to high depressive symptoms group.

The area under the ROC curve for the regression with depression as the dependent variable was .87 (95% CI, .81 to .93), which is an indicator that the model provides an excellent level of discrimination according to Hosmer et al. (2013). See **Appendix G** for corresponding ROC curve graph.

Table 20. Binomial logistic regression of depression on independent variables [$N = 182$]

Step and variable Dependent: Depression	*B*	*SE*	Wald χ^2	*p*	Odds Ratio (e^B)	95% CI for Odds Ratio	
						Lower	Upper
(1) Control variables							
Children with NDD	.29	.27	1.20	.27	1.34	.79	2.28
Child's age	-.02	.05	.13	.72	.98	.89	1.09
Caregiver's age	.04	.04	.73	.39	1.04	.96	1.12
Caregiver's education level	-.08	.22	.12	.73	.93	.60	1.43
Caregiver's annual income	.02	.20	.01	.92	.102	.70	1.50
Caregiver's gender	-.40	.77	.27	.60	.67	.15	3.00
PAS/PUCHS display order	-1.54	.44	12.19	<.01	.22	.09	.51
COVID caregiving	.04	.23	.02	.88	1.04	.66	1.64
COVID therapies	-.01	.37	.00	.99	.99	.48	2.06
COVID financial	.35	.32	2.26	.13	1.41	.90	2.21
Child symptoms/diagnoses	.06	.07	.67	.41	1.06	.93	1.20
Child difficulties	.07	.21	.11	.74	1.07	.72	1.60
Perceived seriousness	.33	.35	1.73	.19	1.39	.85	2.27
Explanatory power	-.37	.15	5.88	.02	.69	.52	.93
Constant	-2.57	1.99	1.71	.19	.08		
(2) Control + Key variables							
Children with NDD	.04	.28	.02	.88	1.04	.61	1.79
Child's age	-.01	.06	.01	.93	1.00	.88	1.12
Caregiver's age	.04	.05	.62	.43	1.04	.94	1.15
Caregiver's education level	.02	.26	.01	.94	1.02	.61	1.70
Caregiver's annual income	-.17	.22	.55	.46	.85	.55	1.31
Caregiver's gender	-.09	.96	.01	.93	.92	.14	5.96
PAS/PUCHS display order	-1.90	.54	12.50	**<.01**	.15	.05	.43
COVID caregiving	.22	.28	.61	.44	1.24	.72	2.16
COVID therapies	-.39	.44	.78	.38	.68	.28	1.61
COVID financial	.37	.27	1.92	.17	1.45	.86	2.47
Child symptoms/diagnoses	.04	.08	.24	.63	1.04	.89	1.22
Child difficulties	.12	.24	.25	.62	1.13	.70	1.81
Perceived seriousness	.28	.29	.93	.33	1.32	.75	2.33
Explanatory power	-.16	.34	.21	.64	.85	.44	1.67
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Chronicity	-.04	.10	.14	.71	.96	.78	1.18
Consequences	-.08	.09	.67	.42	.93	.77	1.11
Personal control	-.10	.07	1.98	.16	.90	.79	1.04
Treatment control	-.03	.10	.12	.73	.97	.80	1.17
Emotional representation	.33	.09	13.51	**<.01**	1.39	1.17	1.66
ES results: VUS vs. pos	-.43	1.05	.17	.68	.65	.08	5.06
Uncertainty	.13	.33	.15	.70	1.14	.60	2.17
Constant	-4.34	4.12	1.11	.29	.01		

Note: Cox & Snell $R^2 = .34$. Nagelkerke $R^2 = .49$. Hosmer & Lemeshow goodness-of-fit test: $\chi^2(8) = 7.22$, $p = .51$.
Highlighted values signify statistically significant coefficients at $p \leq .002$.

Anxiety. A hierarchical binomial logistic regression was performed to ascertain the effects of five illness representation dimensions (chronicity, consequences, personal control, coherence, and emotional representation), the VUS-versus-positive ES results comparison, and total weighted uncertainty on the likelihood that participants have mild to severe signs of anxiety ($N = 41$). Linearity of the continuous variables with respect to the logit (log odds transformation) of the dependent variable was assessed via the Box-Tidwell (1962) procedure. Please refer to the Adaptation section for a description of this procedure and its parameters.

As with the logistic regressions on adaptation and depression, a Bonferroni correction was applied using all 21 terms in the model, resulting in statistical significance for the linearity assumption testing being accepted when $p \leq .002$, obtained by dividing the significance threshold of $p = .05$ by 22 (Tabachnick & Fidell 2014; Laerd Statistics 2017b). Based on this assessment, all continuous independent variables were found to be linearly related to the logit of the dependent variable based on p values greater than .002. As before, this adjusted significance level of $p \leq .002$ from the Bonferroni correction was used to determine the statistical significance of individual coefficients in the logistic regression model.

The 14 control variables were entered into the regression model in Step 1, followed by the seven key predictor variables in Step 2. The final logistic regression model reached statistical significance, $\chi^2(21) = 49.20$, $p < .01$. The model correctly classified 85.4% of cases. Sensitivity was 51.7%, specificity was 93.9%, positive predictive value was 68.2%, and negative predictive value was 88.5%. The overall predictive power of the model improved by 12.8% (Nagelkerke R^2 33.6% to 46.4%) from Step 1 to Step 2 by adding the set of seven predictor variables.

Of the 21 independent variables, none reached statistical significance based on the Bonferroni adjusted p value of .002. However, two of the control variables (caregiver's annual

income and change to caregiving activities during COVID) and one of the key variables (emotional representation) displayed trends (see **Table 21**). While holding other covariates at a constant value, increasing annual income by one unit (moving from one income range to the next highest) was associated with an 83% higher likelihood of being in the group reporting anxiety symptoms beyond the normal range. Additionally, moving from one caregiving category to the next (indicating *decreasing* time spent caring for one's child during COVID) was associated with 55% lower likelihood of being in the higher anxiety group. Finally, a one-point increase on the emotional representation scale was associated with a 27% increase in the odds of being in the mild to high anxiety group.

The area under the ROC curve for the regression with anxiety as the dependent variable was .88 (95% CI, .81 to .95), which is an indicator that the model provides an excellent level of discrimination according to Hosmer et al. (2013). See **Appendix G** for corresponding ROC curve graph.

Table 21. Binomial logistic regression of anxiety on independent variables [$N = 182$]

Step and variable Dependent: Anxiety	*B*	*SE*	Wald χ^2	*p*	Odds Ratio (e^B)	95% CI for Odds Ratio	
						Lower	Upper
(1) Control variables							
Children with NDD	.55	.27	4.22	.04	1.74	1.03	2.95
Child's age	.02	.06	.11	.74	1.02	.91	1.14
Caregiver's age	-.03	.05	.39	.53	.97	.89	1.07
Caregiver's education level	-.43	.24	3.17	.08	.65	.41	1.04
Caregiver's annual income	.63	.24	6.57	.01	1.87	1.16	3.02
Caregiver's gender	-.28	.82	.12	.73	.76	.15	3.76
PAS/PUCHS display order	-.29	.48	.36	.55	.75	.29	1.93
COVID caregiving	-.65	.25	6.77	.01	.52	.32	.85
COVID therapies	.12	.41	.09	.77	1.13	.50	2.54
COVID financial	.39	.26	2.17	.14	1.47	.88	2.46
Child symptoms/diagnoses	.34	.22	2.44	.12	1.41	.92	2.17
Child difficulties	.10	.08	1.63	.20	1.11	.95	1.30
Perceived seriousness	.50	.31	2.65	.10	1.65	.90	3.01
Explanatory power	-.37	.17	4.95	.03	.69	.50	.96
Constant	-1.78	2.17	.67	.41	.17		
(2) Control + Key variables							
Children with NDD	.35	.27	1.69	.19	1.42	.84	2.42
Child's age	.03	.06	.15	.70	1.03	.91	1.16
Caregiver's age	-.03	.05	.28	.60	.97	.87	1.08
Caregiver's education level	-.39	.28	2.01	.16	.68	.39	1.16
Caregiver's annual income	.47	.26	3.21	.07	1.60	.96	2.69
Caregiver's gender	-.17	.97	.03	.86	.84	.13	5.63
PAS/PUCHS display order	-.25	.57	.19	.66	.78	.26	2.38
COVID caregiving	-.63	.29	4.76	**.03**	.53	.30	.94
COVID therapies	-.21	.47	.19	.66	.81	.32	2.04
COVID financial	.30	.29	1.04	.31	1.35	.76	2.39
Child symptoms/diagnoses	.39	.26	2.30	.13	1.48	.89	2.45
Child difficulties	.12	.09	1.75	.19	1.13	.95	1.34
Perceived seriousness	.36	.34	1.08	.30	1.43	.73	2.79
Explanatory power	-.26	.37	.48	.49	.77	.37	1.60
--							
Chronicity	.09	.13	.53	.47	1.10	.86	1.41
Consequences	-.10	.10	.84	.36	.91	.74	1.11
Personal control	-.03	.07	.26	.61	.97	.85	1.10
Coherence	.04	.06	.34	.56	1.04	.92	1.17
Emotional representation	.26	.09	8.83	**<.01**	1.29	1.09	1.53
ES results: VUS vs. pos	-.48	1.09	.20	.66	.62	.07	5.23
Uncertainty	.26	.36	.51	.48	1.29	.64	2.60
Constant	-6.17	4.12	2.24	.14	.00		

Note: Cox & Snell $R^2 = .30$. Nagelkerke $R^2 = .46$. Hosmer & Lemeshow goodness-of-fit test: $\chi^2(8) = 8.03$, $p = .43$.
Highlighted values signify statistically significant coefficients at $p \leq .002$.

Stress. A hierarchical binomial logistic regression was performed to ascertain the effects of five illness representation dimensions (consequences, personal control, coherence, emotional representation, and genetic causal attribution), the VUS-versus-positive ES results comparison, and total weighted uncertainty on the likelihood that participants have mild to severe signs of anxiety ($N = 70$). Linearity of the continuous variables with respect to the logit (log odds transformation) of the dependent variable was assessed via the Box-Tidwell (1962) procedure. Please refer to the Adaptation section for a description of this procedure and its parameters.

As with the logistic regressions on adaptation, depression, and anxiety, a Bonferroni correction was applied using all 21 terms in the model, resulting in statistical significance for the linearity assumption testing being accepted when $p \leq .002$, obtained by dividing the significance threshold of $p = .05$ by 22 (Tabachnick & Fidell 2014; Laerd Statistics 2017b). Based on this assessment, all continuous independent variables were found to be linearly related to the logit of the dependent variable based on p values greater than .002. As before, this adjusted significance level of $p \leq .002$ from the Bonferroni correction was used to determine the statistical significance of individual coefficients in the logistic regression model.

The 14 control variables were entered into the regression model in Step 1, followed by the seven key predictor variables in Step 2. The final logistic regression model reached statistical significance, $\chi^2(21) = 43.60$, $p < .01$. The model correctly classified 79.2% of cases. Sensitivity was 61.5%, specificity was 89.1%, positive predictive value was 76.2%, and negative predictive value was 67.2%. The overall predictive power of the model improved by 16.9% (Nagelkerke R^2 19.7% to 36.6%) from Step 1 to Step 2 by adding the set of seven predictor variables.

Of the 21 independent variables, none reached statistical significance based on the Bonferroni adjusted p value of .002. However, the analysis yielded a trend in one variable,

emotional representation (see **Table 22**). A one-point increase on the emotional representation scale, while holding other covariates at a constant value, was associated with a 22% increase in the odds of being in the group reporting signs of stress beyond the normal range.

The area under the ROC curve for the regression with stress as the dependent variable was .81 (95% CI, .74 to .89), which is an indicator that the model provides an excellent level of discrimination according to Hosmer et al. (2013). See **Appendix G** for corresponding ROC curve graph.

Table 22. Binomial logistic regression of stress on independent variables [$N = 182$]

Step and variable Dependent: Stress	*B*	*SE*	Wald χ^2	*p*	Odds Ratio (e^B)	95% CI for Odds Ratio	
						Lower	Upper
(1) Control variables							
Children with NDD	-.28	.34	.67	.41	.76	.39	1.48
Child's age	.01	.05	.02	.09	1.01	.92	1.10
Caregiver's age	.04	.04	1.07	.30	1.04	.97	1.11
Caregiver's education level	-.03	.19	.03	.88	.97	.67	1.41
Caregiver's annual income	.01	.17	.38	.54	1.11	.80	1.55
Caregiver's gender	-.17	.68	.06	.80	.84	.22	3.22
PAS/PUCHS display order	-.24	.38	.40	.53	.79	.37	1.66
COVID caregiving	.01	.21	.00	.95	1.01	.68	1.52
COVID therapies	.46	.33	1.95	.16	1.59	.83	3.04
COVID financial	.45	.20	5.08	.02	1.57	1.06	2.32
Child symptoms/diagnoses	.10	.18	.28	.60	1.10	.77	1.57
Child difficulties	.07	.06	1.17	.28	1.07	.95	1.20
Perceived seriousness	.12	.22	.27	.60	1.12	.72	1.74
Explanatory power	-.21	1.3	2.82	.09	.81	.63	1.04
Constant	-3.72	4.36	4.36	.04	.02		
(2) Control + Key variables							
Children with NDD	-.64	.50	1.65	.20	.53	.20	1.40
Child's age	.02	.05	.21	.65	1.02	.93	1.13
Caregiver's age	.04	.04	1.00	.32	1.04	.96	1.13
Caregiver's education level	.05	.21	.05	.82	1.05	.69	1.59
Caregiver's annual income	-.04	.19	.05	.82	.96	.66	1.39
Caregiver's gender	.02	.81	.00	.89	1.02	.21	4.99
PAS/PUCHS display order	-.25	.43	.35	.56	.78	.33	1.80
COVID caregiving	.06	.24	.06	.80	1.06	.66	1.70
COVID therapies	.23	.37	.39	.53	1.26	.61	2.62
COVID financial	.40	.22	3.27	.07	1.50	.97	2.31
Child symptoms/diagnoses	.09	.20	.18	.67	1.09	.73	1.63
Child difficulties	.04	.07	.38	.54	1.04	.92	1.19
Perceived seriousness	.12	.25	.24	.62	1.13	.69	1.86
Explanatory power	-.11	.28	.15	.70	.90	.52	1.56
--							
Consequences	-.03	.07	.13	.72	.97	.84	1.13
Personal control	-.05	.05	.90	.34	.85	.86	1.05
Coherence	.06	.05	1.46	.28	1.06	.97	1.16
Emotional representation	.23	.07	11.85	**<.01**	1.25	1.10	1.42
Genetic causal attribution	-.09	.18	.23	.63	.92	.65	1.30
ES results: VUS vs. pos	-.06	.84	.01	.94	.94	.18	4.93
Uncertainty	.45	.28	2.53	.11	.16	.90	2.71
Constant	-6.76	2.59	6.82	.01	.00		

Note: Cox & Snell $R^2 = .27$. Nagelkerke $R^2 = .37$. Hosmer & Lemeshow goodness-of-fit test: $\chi^2(8) = 8.33$, $p = .40$.
Highlighted values signify statistically significant coefficients at $p \leq .002$.

Aim 3: Time in Relation to NDD Appraisals, Adaptation, and Affective Outcomes

Hypothesis 3.1

Univariate logistic regression analyses were conducted between each of the two time variables (Time Since Exome Sequencing (ES) and Time Since Clinical Attention (CA)) and each of the four outcome variables (adaptation, depression, anxiety, and stress). For Time Since ES, the range was 0 to 17 years, with a mean of 3.2 years. For Time Since CA, the range was 0 to 40 years, with a mean of 10.5 years. The distributions of both time variables were strongly positively skewed, with a relatively high proportion of respondents' children having undergone ES and received clinical attention more recently (see **Figure 2**). None of these relationships were statistically significant (see **Table 16** in the preceding section).

Each logistic regression model from Aim 2 was completed two additional times, adding one of the two time variables in each as part of Step 2. The Nagelkerke R^2, correct classification percentage, and chi-square values were compared between the models without and with each time variable to determine if the addition of time improved the model, and if the time variable emerged as a significant predictor of the outcome variable (see **Table 23**).

In the regression with adaptation as the dependent variable, adding the Time Since ES variable to the model improved the classification accuracy, but marginally lowered the Nagelkerke R^2. In the regression with depression as the dependent variable, adding the Time Since ES variable to the model slightly improved classification accuracy and variance in depression explained by the model. This same pattern was observed in the regressions on anxiety and stress.

In the regression with adaptation as the dependent variable, adding the Time Since CA variable to the model mildly improved the Nagelkerke R^2, but marginally lowered the

classification accuracy. In the regression with depression as the dependent variable, adding Time Since CA did not alter the Nagelkerke R^2 of the model and marginally improved classification accuracy. In the regressions with anxiety and stress as the dependent variables, the addition of Time Since CA to each model slightly improved both Nagelkerke R^2 and classification accuracy.

In all four of the previously listed models, neither Time Since ES nor Time Since CA was a statistically significant predictor of the outcome. Thus, the hypothesis that greater temporal distance since testing or clinical attention predicts better adaptation was not supported.

Hypothesis 3.2

Because neither time variable was found to be a significant predictor of outcomes, no follow-up moderation analysis was performed.

Table 23. Comparison of logistic regression models with and without inclusion of time variables [$N = 182$]

		B	***p***	**Nagelkerke R^2**	**% correct**	**χ^2 (*p*)**
Adaptation	w/o Time Since ES	--	--	.22	60.7	27.39 (.10)
	w/ Time Since ES	.08	.29	.22	71.4	26.38 (.15)
Depression	w/o Time Since ES	--	--	.48	81.3	58.19 (<.01)
	w/ Time Since ES	-.06	.62	.49	83.0	58.39 (<.01)
Anxiety	w/o Time Since ES	--	--	.46	85.4	49.20 (<.01)
	w/ Time Since ES	.11	.40	.46	86.5	49.31 (<.01)
Stress	w/o Time Since ES	--	--	.36	79.2	43.60 (<.01)
	w/ Time Since ES	.12	.25	.37	79.4	44.62 (<.01)
Adaptation	w/o Time Since CA	--	--	.22	70.7	27.39 (.10)
	w/ Time Since CA	-.16	.24	.23	69.6	27.76 (.12)
Depression	w/o Time Since CA	--	--	.48	81.3	58.19 (<.01)
	w/ Time Since CA	-.08	.57	.48	82.5	57.93 (<.01)
Anxiety	w/o Time Since CA	--	--	.46	85.4	49.20 (<.01)
	w/ Time Since CA	.13	.36	.47	86.0	49.69 (<.01)
Stress	w/o Time Since CA	--	--	.36	79.2	43.60 (<.01)
	w/ Time Since CA	.17	.20	.37	76.9	44.98 (<.01)

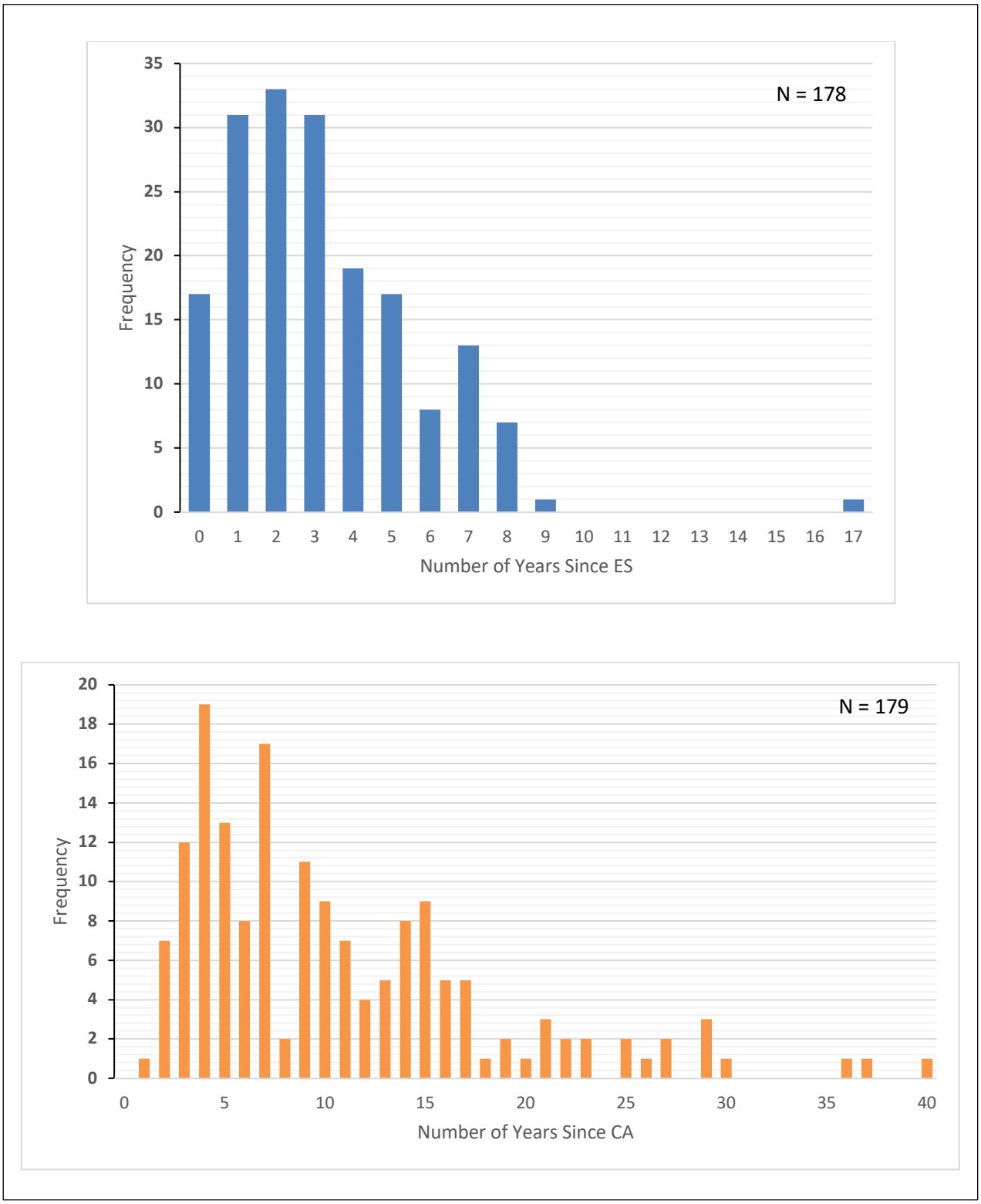


Figure 2. Histograms of self-reported number of years since ES (above) and years since CA (below) and corresponding frequencies.

Supplemental Aims: Predictors of Uncertainty

In addition to the additional aims of the study, we subsequently proposed to address two new specific aims: **1) to investigate how various dimensions of caregivers' NDD-associated uncertainty relate to types of results from ES, and 2) to assess predictors of total uncertainty, including illness representations.** For Supplemental Aim 1, we hypothesized that caregivers whose children received positive ES results would report the lowest levels of uncertainty in all domains, and that caregivers whose children received VUS or negative ES results would report higher levels of uncertainty than caregivers in the positive ES group, but comparable levels of uncertainty to each other. For Supplemental Aim 2, we hypothesized that caregivers who view their child's NDD as less permanent, less controllable, less coherent, and more emotionally distressing would experience greater uncertainty related to their child's condition.

Prior to the following analyses, a series of Shapiro-Wilk normality tests were run for the five dependent variables in this section: total weighted uncertainty (PUCHS score) and its four subscales (medical management, family/reproductive, social, and existential uncertainty). Initially, all variables violated assumptions of normality, Shapiro-Wilk $p < .05$. Multiple transformations, including exclusion of outliers, were run on each uncertainty variable to attempt an approximation to a normal distribution, but these were unsuccessful. Total weighted uncertainty exhibited a ceiling effect with a high proportion of respondents scoring at the low extreme of the scale (0.00), which likely accounted for its non-normal distribution. As such, the raw untransformed variables were used in subsequent analyses with the caveat that they deviated from normality.

Uncertainty Experience (PUCHS Part A) vs. Importance (Part B)

Two one-way ANOVA were run to clarify whether inter-ES results group differences on uncertainty were driven by responses to Part A of the PUCHS (uncertainty experienced) or to Part B (importance of resolving uncertainty). The ES groups were found to be significantly different on Part A of the PUCHS, $F(2,180) = 8.76$, $p < .01$. However, there were no significant differences between ES results groups observed for Part B, $F(2,180) = .70$, $p = .50$ (see **Table 24**).

Supplemental Aim 1: Relationship Between ES Result and Domains of Uncertainty

A series of one-way ANOVA were conducted to determine if the four domains or subtypes of uncertainty were different across the three ES results groups. Participants experienced moderate levels of uncertainty in the PUCHS components, feeling the *most* weighted uncertainty about issues related to social life and the *least* weighted uncertainty about issues related to treatment.

For each analysis, outliers were assessed by inspection of a box-plot and homogeneity of variances was assessed by Levene's test. All analyses passed the assumption of homogeneity of variances, shown below in **Table 25(a)**. Post-hoc comparisons are shown in **Table 25(b)**.

For uncertainty related to medical management, $F(2,180) = 4.13$, $p = .02$, PUCHS subscale score increased from the positive ($1.37 \pm .94$) to the negative ($1.76 \pm .92$) and VUS (1.83 ± 1.12) results group, in that order, indicating the highest levels of perceived uncertainty for those who reported receiving VUS results (see **Table 25(a)**). Tukey-Kramer post-hoc analysis revealed a statistically significant increase from positive ES result to VUS (.45, 95% CI (.02 to .88), $p = .04$) (see **Table 25(b)**).

For family/reproductive uncertainty, $F(2,180) = 12.92$, $p < .01$, PUCHS subscale score increased from the positive (1.15 ± .93) to the negative (1.69 ± 1.03) and VUS (2.06 ± 1.04) results group, in that order, indicating the highest levels of perceived uncertainty for those who reported receiving VUS results (see **Table 25(a)**). Tukey-Kramer post-hoc analysis revealed a statistically significant increase from positive to negative ES result (.54, 95% CI (-.01 to .78), $p <$ .01), as well as the increase from positive ES result to VUS (.91, 95% CI (.47 to 1.35), $p < .01$) (see **Table 25(b)**).

Finally, for social uncertainty, $F(2,180) = 3.55$, $p = .03$, PUCHS subscale score increased from the positive ES (1.78 ± 1.33) to the negative ES (2.22 ± 1.29) and VUS (2.40 ± 1.35) results group, in that order, indicating the highest levels of perceived uncertainty for those who reported receiving VUS results (see **Table 25(a)**). Tukey-Kramer post-hoc analysis revealed that a statistically significant increase from positive to VUS (.60, 95% CI (.02 to 1.19), $p = .04$) (see **Table 25(b)**).

Table 24. One-way ANOVA of PUCHS Parts A and B by ES results group [*N* = 182]

Outcome Variable	ES Results Group						Equality of variances (Levene)
	Total	Positive (*N* = 81)	Negative (*N* = 59)	VUS (*N* = 42)			
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*F*	*p*	
PUCHS Part A (Uncertainty Experienced)	1.69 (.83)	1.42 (.81)	1.81 (.73)	1.98 (.85)	8.76	**<.01**	Passed (*p* = .47)
PUCHS Part B (Weight (Importance))	4.09 (.55)	4.12(.54)	4.02 (.53)	4.13(.61)	.70	.50	Passed (*p* = .73)

Note: Bolded values represent statistically significant contrasts at $p \leq .05$.

Table 25(a): One-way ANOVA of total uncertainty and uncertainty subscales by ES results group [*N* = 182]

PUCHS Outcome Variable	ES Results Group						Equality of variances (Levene)
	Total	Positive (*N* = 81)	Negative (*N* = 59)	VUS (*N* = 42)			
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	*F*	*p*	
Total (From **Table 17(a)**)	1.59 (.88)	1.32 (.85)	1.76 (.85)	1.92 (.87)	8.32	**<.01**	Passed (*p* = .80)
Medical Management	1.61 (.98)	1.37 (.94)	1.76 (.92)	1.83 (1.12)	4.13	**.02**	Passed (*p* = .17)
Family/ Reproductive	1.52 (1.05)	1.15 (.93)	1.69 (1.03)	2.06 (1.04)	12.92	**<.01**	Passed (*p* = .18)
Social	2.03 (1.33)	1.78 (1.33)	2.22 (1.29)	2.40 (1.35)	3.55	**.03**	Passed (*p* = .81)
Existential	1.00 (1.12)	.96 (1.10)	1.11 (1.21)	.94 (1.05)	.38	.68	Passed (*p* = .61)

Note: Bolded values represent statistically significant contrasts at $p \leq .05$.

TABLE 25(b): Tukey-Kramer post-hoc tests for pairwise comparisons of uncertainty by ES results group [$N = 182$]

PUCHS Outcome Variable	Contrast	Mean Difference (*p*)	*SE*	95% Confidence Interval	
				Lower	Upper
Total (From **Table 17(b)**)	VUS vs. positive	**.60 (<.01)**	.16	.22	.99
	VUS vs. negative	.16 (.17)	.17	-.25	.57
	Positive vs. negative	**.44 (<.01)**	.15	.09	.79
Medical Management	VUS vs. positive	**.45 (.04)**	.18	.02	.88
	VUS vs. negative	.06 (.95)	.20	-.40	.52
	Positive vs. negative	.39 (.05)	.17	-.01	.78
Family/ Reproductive	VUS vs. positive	**.91 (<.01)**	.19	.47	1.35
	VUS vs. negative	.37 (.16)	.20	-.10	.83
	Positive vs. negative	**.54 (<.01)**	.17	.14	.94
Social	VUS vs. positive	**.60 (.04)**	.25	.02	1.19
	VUS vs. negative	.17 (.80)	.26	-.46	.79
	Positive vs. negative	.44 (.13)	.23	-.10	.97
Existential	N/A (no significant differences found across ES groups)				

Note: Bolded values represent statistically significant contrasts at $p \leq .05$.

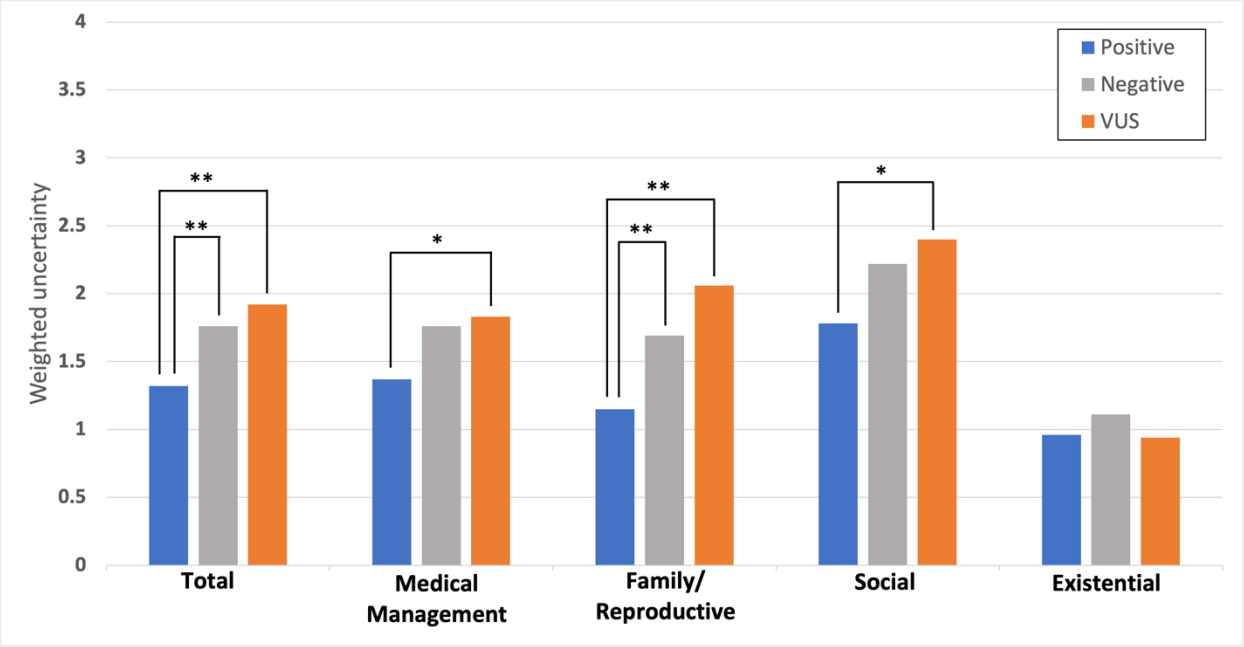


Figure 3. Mean scores of total and subtypes of uncertainty by ES results group. Range of possible scores is 0 to 4. * $p < .05$, ** $p < .01$.

Supplemental Aim 2: Predictors of Total Uncertainty

The same dichotomous uncertainty variable from Aim 2 was used as the dependent variable for the logistic regression. This variable was dichotomized using a median split, wherein values up to and including the median value from the PUCHS (1.51) were categorized as 0/"low" and values greater than 1.51 were categorized as 1/"high". The median for the sub-sample (N = 182) was equivalent to the median of the original sample (N = 190).

To determine which key variables would be included in the logistic regression model, a series of univariate logistic regression analyses between the 12 key variables of interest and the dichotomized uncertainty variable. Any relationships that displayed significance at $p \leq .30$ were included in the following hierarchical regression model (see **Table 26**).

A hierarchical binomial logistic regression was performed to ascertain the effects of five illness representation dimensions (personal control, coherence, cyclicity, emotional representation, and genetic attribution), the VUS-versus-negative ES results comparison, and the VUS-versus-positive ES results comparison on the likelihood that participants have higher levels of uncertainty. Multicollinearity diagnostics were run on the variables in a multiple linear regression analysis; because time since clinical attention and child's age yielded a variance inflation factor (VIF) greater than 10, they were excluded from the logistic regression model. Linearity of the continuous variables with respect to the logit (log odds transformation) of the dependent variable was assessed via the Box-Tidwell (1962) procedure. As part of this procedure, all continuous predictor variables were transformed into their natural logs (ln(variable)). Then, interaction terms between the predictor variable and its natural log were created (variable * ln(variable)) and entered into the regression model along with the untransformed predictor variables. Per the Box-Tidwell guidance, if these interactions terms *fail*

to reach statistical significance, then the assumption of linearity is upheld (Laerd Statistics 2017b).

In addition, as with the previous logistic regression models, a Bonferroni correction was applied using all 20 terms in the model resulting in statistical significance being accepted when $p \leq .003$ (Tabachnick & Fidell 2014; Laerd Statistics 2017b). Based on this assessment, all continuous independent variables were found to be linearly related to the logit of the dependent variable based on p values greater than .003. This adjusted significance level of $p \leq .003$ from the Bonferroni correction was used to determine the statistical significance of individual coefficients in the logistic regression model.

The 13 control variables were entered into the regression model in Step 1, followed by the seven key predictor variables in Step 2. The final logistic regression model reached statistical significance, $\chi^2(20) = 65.04$, $p < .01$. The model correctly classified 76.9% of cases. Sensitivity was 76.3%, specificity was 77.6%, positive predictive value was 78.2% and negative predictive value was 75.6%. The overall predictive power of the model improved by 8.2% (Nagelkerke R^2 40.7% to 48.9%) from Step 1 to Step 2 by adding the set of six predictor variables.

Of the 20 independent variables, none reached statistical significance based on the Bonferroni adjusted p value of .003. However, two variables (coherence and caregiver's age) displayed trends (see **Table 27**). Increasing sense of coherence for the child's NDD was associated with a decreased likelihood of experiencing above-average uncertainty; in other words, greater coherence was associated with greater certainty. Increasing caregiver age was associated with a decreased likelihood of experiencing above-average uncertainty; in other words, older caregivers felt more certainty about their child's condition.

The area under the ROC curve was .85 (95% CI, .79 to .91), which is an indicator that the model provides an excellent level of discrimination according to Hosmer et al. (2013). See **Appendix G** for corresponding ROC curve graph.

Table 26. Betas and *p*-values for univariate logistic regressions of dichotomized uncertainty on predictor variables [*N* = 182]

Variable[†]	**Uncertainty *B* (*p*)**
Children with NDD	.13 (.49)
Child's age	-.02 (.32)
Caregiver's age	-.03 (.04)
Caregiver's education	-.43 (<.01)
Caregiver's income	-.18 (.12)
Caregiver's gender	-.10 (.84)
PAS/PUCHS display order	-.27 (.35)
COVID caregiving	-.12 (.42)
COVID therapies	.21 (.37)
COVID financial	.41 (.01)
Child symptoms/diagnoses	-.01 (.95)
Child difficulties	.00 (.94)
Perceived seriousness	-.02 (.85)
Explanatory power	-.52 (<.01)
Chronicity	-.03 (.44)
Consequences	.01 (.77)
Personal control	**-.06 (.06)**
Treatment control	-.00 (.92)
Coherence	**-.15 (<.01)**
Cyclicity	**.07 (.05)**
Emotional representation	**.09 (.01)**
Genetic attribution	**-.16 (.21)**
Time since exome testing	.02 (.70)
Time since clinical attention	**-.03 (.19)**
VUS vs. positive	**-1.26 (<.01)**
VUS vs. negative	**.75 (.02)**

[†] Relationships that are statistically significant at $p \leq .30$ are bolded in the corresponding cell of the table. Note that all control variables ("children with NDD through "explanatory power") were included in subsequent regression models regardless of statistical significance.

Table 27. Binomial logistic regression of uncertainty on independent variables [$N = 182$]

Step and variable Dependent: Uncertainty	***B***	***SE***	**Wald χ^2**	***p***	**Odds Ratio (e^B)**	**95% CI for Odds Ratio Lower---Upper**	
(1) Control variables							
Children with NDD	.33	.25	1.69	.19	1.39	.85	2.29
Caregiver's age	-.05	.03	2.71	.10	.95	.90	1.01
Caregiver's education level	-.61	.21	8.21	<.01	.55	.36	.83
Caregiver's annual income	.16	.17	.89	.35	1.18	.94	1.65
Caregiver's gender	-.09	.74	.01	.91	.92	.22	3.88
PAS/PUCHS display order	-.64	.40	2.54	.11	.53	.24	1.16
COVID caregiving	-.36	.22	2.61	.11	.70	.45	1.08
COVID therapies	.27	.33	.66	.42	1.31	.89	2.50
COVID financial	.24	.21	1.33	.25	1.27	.85	1.90
Child symptoms/diagnoses	.23	.19	1.45	.23	1.25	.87	1.81
Child difficulties	.05	.06	.71	.40	1.05	.93	1.19
Perceived seriousness	-.15	.22	.45	50	.86	.56	1.33
Explanatory power	-.63	.14	19.76	<.01	.53	.40	.70
Constant	4.90	1.84	7.12	.01	134.32		
(2) Control + Key variables							
Children with NDD	-.22	.28	.62	.43	1.25	.72	2.18
Caregiver's age	-.07	.04	3.56	**.05**	.94	.88	1.00
Caregiver's education level	-.54	.23	5.57	.12	.58	.37	.91
Caregiver's annual income	-.19	.19	.99	.32	1.20	.84	1.74
Caregiver's gender	.13	.82	.02	.88	1.13	.23	5.64
PAS/PUCHS display order	-.81	.45	3.29	.07	.45	.19	1.07
COVID caregiving	-.44	.24	3.29	.07	.64	.40	1.04
COVID therapies	.16	.36	.19	.66	1.17	.58	2.36
COVID financial	.26	.22	1.32	.25	1.29	.83	2.01
Child symptoms/diagnoses	.21	.20	1.18	.38	1.24	.84	1.82
Child difficulties	.02	.07	.09	.77	1.02	.89	1.17
Perceived seriousness	-.25	.25	1.05	.31	.78	.48	1.26
Explanatory power	-.31	.32	.94	.33	.73	.39	1.38
--							
Personal control	-.07	.05	1.83	.18	.93	.84	1.03
Coherence	-.11	.05	4.89	**.03**	.90	.82	.99
Cyclicity	.03	.06	.39	.53	1.04	.93	1.15
Emotional representation	.06	.05	1.34	.25	1.06	.96	1.16
Genetic causal attribution	-.12	.18	.40	.53	.89	.63	1.27
ES results: VUS vs. pos	-.49	1.18	.17	.68	.61	.06	6.15
ES results: VUS vs. neg	.38	.65	.34	.56	1.46	.41	5.18
Constant	7.25	2.53	8.22	.00	1402.06		

Note: Cox & Snell $R^2 = .37$. Nagelkerke $R^2 = .49$. Hosmer & Lemeshow goodness-of-fit test: $\chi^2(8) = 5.86$, $p = .66$.

Bolded values signify coefficients with $p \leq .05$ considered to be trends in the data, which are discussed in more detail in the text.

The variables of child's age and time since clinical attention were initially included in regression analysis, but excluded following collinearity diagnostics indicating VIF > 10 for multiple linear regression.

DISCUSSION

Summary of Findings

Relationship Between ES Results and Illness Representations

We hypothesized that caregivers would differ in how they perceived their child's NDD based on the type of ES results that were returned. Of the five predictions made about permanence, controllability, coherence, genetic causal attribution, and uncertainty, three were partially supported by the data.

Perceptions of treatment control significantly varied across the levels of ES results in the order predicted: caregivers to children with negative ES results had the strongest perceptions of control over treatments for their child's NDD, followed by those with VUS results and finally those with positive results. However, the only statistically significant difference found was between the means of the positive ES results and negative ES results groups. Across types of ES results, caregivers in our sample had fairly poor perceptions of treatment control (mean: 14.30 ± 4.00 out of 25), lower than those of parents of children with ASD in previous research. Specifically, Al Anbar et al. (2010, $N = 89$), Gatzoyia et al. (2014, $N = 111$), and Mire et al. (2017, $N = 68$) reported treatment control means of 17.6 ± 3.3, 19.34[1] ± 2.17, and 19.68 ± 3.00 on the IPQ-RA, respectively. These varying perceptions of treatment control between the current and past studies may be attributed to inherent differences in sample size and composition (e.g., families with ASD only vs. a range of NDD), or other factors not measured.

[1] For the purposes of comparison here, mean IPQ-RA scores from the study by Gatzoyia et al. (2014) were transformed and standardized to match the range of the traditional IPQ-R(A) (5 to 25). The original scores reported by the authors were collected on a scale ranging from 0 to 10.

Caregivers' subjective degree of coherence about their child's condition differed between ES results categories, but deviated from the anticipated order. In the illness representations framework, coherence refers to the extent to which caregivers believe they understand their child's diagnosis. Caregivers to children with positive ES results reported the highest levels of coherence, followed by those with negative results, and finally those with VUS results. The mean difference between the highest coherence ES group (positive) and the middle coherence ES group (negative) was statistically significant, but the difference between the negative ES group and the lowest coherence group (VUS) was not. Caregivers' perceptions of coherence in our study fall on the lower end of the range of mean coherence scores from the three prior studies mentioned in the paragraph above (Al Anbar et al: 18.3 ± 4.0, Gatzoyia et al: 21.66 ± 1.81, Mire et al.: 16.41 ± 3.94), and reflect moderately low levels of coherence (mean: 16.75 ± 4.98 out of 25). We can infer that obtaining a diagnosis or explanation through ES facilitates caregivers making sense of their child's condition. Although not shown in the preceding data tables, this conclusion is supported by a statistically significant correlation between coherence and the extent to which caregivers endorsed the ES result as explaining their child's differences ($r(180) = .41$, $p < .001$).

Contrary to what we expected, perceptions of NDD chronicity did not differ based on category of ES results, though the data did trend in the direction hypothesized. Our findings were inconsistent with those from past studies in which parents who received positive/diagnostic genetic results related to ASD saw their child's condition as more permanent (Reiff et al. 2017). Caregiver perceptions of NDD permanence were notably higher across result types in our study than those of parent participants in the study by Reiff's team (means: 26.93 ± 3.48 out of 30 and

3.94[2] out of 5, respectively). This discrepancy may be attributable to differences in measurement, sample characteristics, and/or time since genetic testing. Reiff and colleagues assessed perceptions of permanence with a single question, as opposed to the six-item IPQ-RA chronicity subscale in our study. Their sample was restricted to children with a clinical diagnosis of ASD, compared to the current study sample representing a range of NDD. Furthermore, the characteristics of the 2017 study sample with respect to testing timeline are unclear. The majority of participants had received genetic test results in the past two years. For the smaller proportion of respondents outside the two-year range, number of years since testing was not specified (stated only as "25+ months"). Time since presentation of child's ASD symptoms was also not reported.

Similarly, no significant differences were observed in perceptions of consequences, personal control, cyclicity, or emotional representation of the NDD. However, based on past research with caregivers of children with ASD, perceived permanence and perceived modifiability of the disorder by treatment are closely and inversely related (Reiff et al. 2017). Because treatment control perceptions were found to differ by ES results, our study nevertheless supplies evidence that ES results influence how caregivers view the capacity of therapies to help their child, which has potentially wide-reaching clinical implications.

Interestingly, caregivers across the three ES results groups reported comparable endorsement of genetics/heredity as the cause of their child's NDD (mean: 4.03 ± 1.16 out of 5). The same pattern was previously observed in parents receiving CMA results for ASD, which the authors reasoned was indicative of parents integrating the genetic results into their existing framework of causal understandings rather than constructing a new belief system (Reiff et al.

[2] Standard deviations not reported

2017). This suggests that it is not necessarily the belief in an underlying molecular origin for the NDD that drives the relationships described above. It is possible that there are cognitive and affective mediators that were not explicitly measured in the current study.

We also hypothesized that uncertainty would moderate the relationship between ES results and illness representations. The interaction terms in the two-way ANOVA of ES results by uncertainty on the IPQ-RA dimensions revealed no evidence of a moderating effect, as all failed to reach statistical significance. As such, it appears that the strength of the relationship between category of genetic test result and illness representations does not appreciably differ by the level of perceived uncertainty. It is also possible that the variable configuration in a true moderation relationship, if it exists, is distinct from that proposed in the current study. For example, illness perceptions could be a moderator between ES results and uncertainty. This prediction would be justifiable from the theoretical standpoint of the Transactional Model of Stress and Coping given that illness perceptions and uncertainty both constitute appraisals, and the literature so far is unclear as to how these constructs interrelate in the context of caring for a child with a chronic condition. Testing this alternate moderation hypothesis would have been unwieldy in our study, due to the number of distinct variables corresponding to the eight IPQ-RA subscales and the need to stratify each. However, future research projects could elect to use an abbreviated measure of illness representations, such as the Brief Illness Perception Questionnaire (Broadbent et al. 2006), which would facilitate the investigation of illness perceptions as a potential moderator between genetic results and uncertainty related to the child's NDD.

Relationship Between ES Results and Uncertainty

Mean uncertainty from the PUCHS (1.59 ± .88 [range 0 to 4]) signaled that, on the whole, respondents in our sample experienced middling uncertainty related to their child's NDD.

Levels of uncertainty were similar to those reported by Bell and colleagues (2019) (-.72 ± .78 [range -2 to 2]) among mothers of children with Duchenne or Becker muscular dystrophy. However, caregivers in the current study had markedly lower average levels of uncertainty relative to past studies with parents of children with undiagnosed medical conditions (Macnamara 2014: .66 ± .76 [range -2 to 2]; Umstead et al. n.d.: .77 ± .82 [range -2 to 2]; Yanes et al. 2017: 3.60 ± .99 [range 1 to 5]). Thus, it is important to note that even though differences were found across the three ES results groups, caregivers were overall only moderately uncertain about the implications and significance of their child's condition.

Weighted uncertainty differed significantly among participants based on ES results, indicating that uncertainty appears to be an important illness appraisal affected by new information from ES testing. The ES groups fell in the expected order: caregivers who reported receiving a VUS experienced more uncertainty in domains that were important to them than did those who reported receiving negative or positive ES results. VUS results from ES are steeped in uncertainty, providing information about genetic changes that may or may not ultimately have clinical significance or provide an explanation for the child's condition (Kiedrowski et al. 2016; Timmermans, Tietbohl & Skaperdas 2016). Post-hoc analyses revealed that it was the perceived uncertainty (measured by Part A of the PUCHS) that drove the intergroup differences, rather than caregivers' perceived value of resolving different types of uncertainty (indicated by the weights on Part B of the PUCHS). In fact, caregivers across ES groups were similar in how they assessed the importance of certainty in their child's NDD, but the degree to which they perceived that certainty hinged on ES findings.

Uncertainty related to medical management was relatively low across all respondents, suggesting that caregivers on the whole feel somewhat equipped to visit a provider and discuss

therapeutic options for their child, and can make some sense of their child's NDD. Uncertainty related to family and reproductive concerns was similarly low, indicating that participants had some understanding of risks to relatives and how to convey this information. Uncertainty related to social support was higher than the previous two domains of uncertainty, though still moderately low, suggesting some doubt about how to connect with other parents in a similar situation. Finally, existential uncertainty was definitively low on average, suggesting that caregivers did not experience pronounced uncertainty related to the purpose or significance of their child's life.

In examining how subtypes of uncertainty varied by ES result category, we found differences in the medical management, family/reproductive, and social dimensions. In all three dimensions, uncertainty levels were highest in the group of caregivers who reported receiving a VUS and lowest in the group who reported positive ES results, and the difference between the most uncertain group (VUS) and least uncertain group (positive ES result) was statistically significant. No significant differences were observed between the positive and negative ES results groups for medical management and social uncertainty.

Regarding uncertainty in medical management, the difference between the positive ES and VUS groups and *lack* of difference between the positive and negative ES results groups may be explained in part by the uniquely ambiguous, muddled nature of VUS. By definition, VUS represent a "residual category" of ES results interpretation: if a variant fails to meet criteria for pathogenic, likely pathogenic, likely benign, or benign designation, it is by default classified as uncertain (Timmermans, Tietbohl & Skaperdas 2016). It is possible that including "uncertain" in the ES result's descriptor subconsciously heightens the recipient's feelings of uncertainty, although no known studies to date have tested hypotheses related to the semantic impact of an

ES result classification. Similarly, there is little empiric evidence to provide further guidance on how outcomes differ between individuals who receive a VUS compared to a negative result from sequencing. Of the existing published studies, most are situated within cancer genetic counseling and concern either how unaffected individuals respond to uninformative results, or how individuals with a known familial variant respond to "true-negative" results (Medendorp et al. 2020). Findings from these scenarios are not closely translatable to our group of caregivers, whose children are clinically affected and for whom no familial variant has been identified.

Furthermore, genetic test-related communication from clinicians may be more discordant for families receiving a VUS compared to a negative result. Variation in how providers disclose VUS and outline corresponding clinical management to cancer patients has been shown to increase patients' feelings of uncertainty (Makhnoon, Shirts & Bowen 2018). Although the authors did not assess the perspectives of patients with (non-VUS) uninformative test results, they suggest that this ambivalence is unique to VUS. The relevance of this observation to the caregivers with VUS in our sample cannot be ruled out definitively, given that we did not capture post-test communication practices related to findings from ES.

Prior qualitative interviews have found that some families actively construe VUS results as actionable and diagnostic, either through misinterpreting the information or desiring actionability. For these families, the knowledge gained from ES testing, though uncertain, motivated them to monitor their condition more proactively (Werner-Lin et al. 2017). The researchers proposed that this observation may be reflective of a response to cognitive dissonance, which describes the incompatibility between two cognitions or beliefs. For our participants, we surmise that cognitive dissonance arises from tension between the awareness of some genetic (albeit inconclusive) change and the lack of new treatment options or medical

recommendations. Families who receive a VUS from ES may be more vulnerable to cognitive dissonance and augmented feelings of uncertainty, compared to families who receive a diagnostic or a negative/uninformative result.

Uncertainty related to the availability of social support (parents in a similar situation) was found to significantly differ between caregivers who received a positive ES result compared to a VUS. As with medical management uncertainty, no significant difference was detected between the positive and negative ES results groups. Social support in the context of parenting children with NDD has been broadly studied, with evidence underscoring its protective role in caregivers' psychological wellbeing and quality of life (Halstead et al. 2018). The sense of social uncertainty is enhanced for families who do not get a diagnosis from genetic testing, as reflected in our findings that caregivers with positive results have the lowest perceptions of social uncertainty. Because many patient/family advocacy organizations coalesce around specific diagnoses, families who don't receive a diagnostic test result may face more challenges in reaching those in similar circumstances. Findings from other studies affirm parents' desire for VUS-specific peer support groups as a means of seeking solidarity and comfort from others (Li et al. 2018). Indeed, in the current study and in others focused on children with undiagnosed but suspected genetic conditions (Macnamara 2014; Umstead et al. n.d.), social uncertainty had the highest mean value of all four dimension on the PUCHS. As before with uncertainty related to medical management, we may speculate whether the return of genetic findings reinforces this uncertainty more acutely for caregivers reporting a VUS relative to a negative ES result, but the body of research at present does not offer any compelling explanations.

For uncertainty related to family and reproductive issues, statistically significant differences were observed between the positive ES and VUS results groups, and between the

positive and negative ES results groups. In other words, family/reproductive uncertainty was significantly lower among caregivers who reported receiving positive results from ES than among caregivers who reported receiving VUS or negative results. We posit that this finding relates to the inability of VUS and negative ES results to provide a precise recurrence risk that caregivers can share with family members or incorporate in their own reproductive planning. Moreover, VUS and negative ES results by definition cannot confer a genetic diagnosis, which may be important to caregivers when addressing their family's questions or concerns about the child with NDD (Makela et al. 2009). A diagnosis often constitutes an authoritative label for a set of symptoms, and can allow caregivers to explain their child's problems to others (Yanes et al. 2017; Neustadt 2019). For the caregivers in our study, a genetic diagnosis seemed to carry significance and power that a clinical or developmental diagnosis did not; the majority (73.5%, $N = 75/102$) of our respondents reporting a VUS or negative result on their child's ES indicated that they had already received some kind of diagnosis from a healthcare provider.[3]

Perceptions of existential uncertainty were low overall and did not differ across caregivers with different categories of ES results. It appears that despite experiencing uncertainty in other domains, caregivers did not tend to question the purpose or meaning of their child's life. Their sense of certainty in the significance of their child's life did not hinge on obtaining a genetic diagnosis, which coheres with findings from past research with families with undiagnosed medical conditions (Macnamara 2014).

[3] It is worth noting that some caregivers in our sample may have received a genetic diagnosis from CMA or other genetic testing prior to ES. This was possible due to clinical testing workflows at the recruitment sites and the study eligibility criteria, though numbers of cases were not tracked as part of sample characterization.

Predictors of Uncertainty

In addition to the role of ES results, there were additional variables associated with the level of uncertainty expressed by participants. The analyses of variance (ANOVA) run as part of the moderation testing did reveal several significant associations of high-low dichotomized uncertainty with three illness representation dimensions. Caregivers sorted into the "high uncertainty" group were more likely to express that they experience low personal control, low coherence, and strong negative emotions related to their child's NDD than caregivers in the "low uncertainty" group. These associations align with findings from several past studies. Lipinski and colleagues (2006) found that lower perceived personal control was a significant predictor of high uncertainty among parents of children with rare chromosome conditions. Furthermore, in diverse patient samples, illness uncertainty has been conceptually and empirically linked to emotional distress and mood disturbance (Mast 1998; Johnson Wright, Afari & Zautra 2009; Yanes et al. 2017), so the association with emotional representation was not surprising.

We also investigated the role of illness representations in predicting caregiver uncertainty about their child's NDD when adjusting for other relevant factors. In the full regression model, personal control and emotional representation were not predictive of uncertainty, but coherence and caregiver's age tended toward an association with uncertainty. Younger caregivers in our sample reported higher uncertainty in their child's NDD, in parallel with the relationship found by Lipinski and colleagues (2006). Younger caregivers are more likely to be inexperienced in parenting overall, which then amplifies their lack of knowledge when caring for a child with special needs. They may also be more sensitive to lack of reproductive clarity and recurrence risks as they contemplate having more children, whereas this concern is less salient for older parents who have already completed their families. Other caregiver characteristics like education

level, income, and gender did not significantly explain variance in uncertainty, even though past research has found these to be influential in predicting uncertainty in similar populations (e.g., education level in mothers of children with ASD, Li & Lo 2016).

Predictors of Adaptation

When all control variables and significant key variables were included in the regression model, none succeeded in reaching statistical significance based on the Bonferroni adjusted *p* value. However, trends in the data (as selected by coefficients $p \leq .05$) alluded to possible relationships between adaptation and four variables: personal control, emotional representation, VUS vs. negative ES results category, and caregiver education level.

Personal control, as operationalized in the Illness Perception Questionnaire and its subsequent iterations, captures caregivers' sense that they can effect change in the course of their child's neurodevelopmental condition. It can be viewed as conceptually adjacent to self-efficacy, as both reflect agency and actionability over a particular domain of life (e.g., a medical diagnosis). For the caregivers in our study, perceived control over their child's NDD seemed to bear a possible connection to their adaptation to caring for an affected child.

An interesting trend was that caregivers in the group of individuals who reported a VUS more closely resembled caregivers in the *positive* ES group than in the *negative* ES group in terms of adaptation. In fact, category of ES results turned out to significantly predict adaptation in the full regression model, with caregivers in the VUS group more likely to be well adapted to their child's NDD than those in the negative group.

In a qualitative investigation of parent perspectives of receiving a VUS from microarray testing, Kiedrowski and colleagues (2016) learned that participants distinguished between genetic results as an *answer* versus an *explanation*. Although they cognitively understood that

the VUS result was unclear in terms of pathogenicity, many viewed it as a tentative answer and the "first step toward a unifying diagnosis" (Kiedrowski et al. 2016). Similarly, Bonner (2017) found that some patients receiving VUS from multi-gene cancer panels *felt* that results were more pathogenic, and some less pathogenic, than the information they recalled having been communicated to them by the genetics provider. This subjective appraisal, driven by feeling, more strongly influenced participants' risk perception than the factual clinical messaging. Together, observations from these two studies offer a framework for accounting for possible subtle differences in adaptation between participants who reported receiving VUS results and those who reported receiving negative results in the present study.

Moreover, caregivers whose child received a VUS result may recognize that the result is inherently inconclusive and doesn't negate the uncertainties of their child's condition, a notion supported by our present findings on the elevated levels of uncertainty experienced by families receiving a VUS from ES. Nevertheless, these families may regard the VUS as a partial or possible answer, which can spur movement toward adaptation more so than for caregivers who receive negative ES results and have no genetic information to latch onto, no matter how tenuous. There is recent qualitative evidence that parents of children with ASD and a VUS on genetic testing report improved coping compared to families with other categories of test results (Lucas 2020). In addition, though it was not assessed as a separate outcome variable in our study, ratings of coping efficacy on the PAS were highest for caregivers whose reported a VUS compared to positive and negative ES results (however, these between-group differences were not statistically significant) [data not shown]. Further research is needed to clarify the coping and meaning-making processes associated with uncertain genetic results.

As we predicted, caregivers who had unfavorable feelings related to their child's NDD, as measured by the IPQ-RA emotional representation subscale, reported lower adaptation. Persistent feelings of anxiety, anger, worry, and fear tied to a medical disorder preclude psychologically adapting to and accepting that disorder. Such potent affective experiences likely put a strain on internal coping resources and interfere with the meaning-making and integration processes that are central to adaptation.

Overall uncertainty was not significantly associated with adaptation in univariate analysis and consequently was excluded from the multivariate regression model. We may infer that uncertainty in isolation does not promote or inhibit adaptation. Rather, adaptation unfolds from the ways that uncertainty is appraised and internalized, and this process takes place within the context of the family's diagnostic odyssey. In her influential theory of uncertainty in illness, Mishel (1990) outlined how individuals evaluate uncertainty as either danger or opportunity, which in turn dictates coping response and subsequent outcomes. A previous study involving parents of children with undiagnosed diseases found that uncertainty was strongly negatively associated with coping efficacy (Macnamara 2014), a construct not measured in our study but theoretically residing along the pathway between appraisals and adaptation. We can imagine that there is a broad range of ways in which caregivers in our study construct meaning from the unknowns and the ambiguity in their child's NDD. Because some conceptualize uncertainty as threatening and some as hopeful, and employ corresponding coping strategies, there was no singular predictive relationship between uncertainty and adaptation. A study with parents of children with ASD found a *positive* association between uncertainty in illness and family quality of life, which the author attributed to the catalytic potential of continual uncertainty in promoting positive psychological growth (Garrett 2014). Altogether, current and past data speak to the

presence of important mediating factors between the experience of uncertainty and desirable psychosocial outcomes.

Importantly, there was no association found between the child's reported functional status or NDD severity and caregivers' psychological adaptation. This lack of relationship mirrors past research with mothers of children with Duchenne and Becker muscular dystrophy, which also used the PAS to quantify adaptation (Peay et al. 2016). Although a prevailing assumption may be that families of NDD-diagnosed children with more challenges or clinical comorbidities are "worse off" overall, our results suggest that the medical complexity of a child's NDD on its own does not lead to poorer adaptation. In the same vein, perception of the NDD's seriousness and of the explanatory power of the ES results had no significant association with adaptation in any of the regression models.

Predictors of Depression, Anxiety, and Stress

In the logistic regression models, the only key variable that was significantly associated with the affective outcome variables was emotional representation of the child's NDD ($p \leq .01$). This finding suggests that for caregivers, the negative emotional charge tied to their child's NDD has bearing on their mood and mental health. Conversely, caregivers who are more prone to emotional distress due to psychiatric illness, situational and systemic elements, and other susceptibility factors may be more likely to conceptualize their child's condition as threatening, overemphasize the negative aspects, and experience adverse feelings associated with the NDD as a result.

For anxiety, a few control variables trended toward significance: annual income and COVID-related caregiving change. Respondents with higher annual income and increased caregiving responsibility during the COVID-19 crisis were more likely to fall in the above-

average anxiety group. For depression, one control variable (PAS/PUCHS display order) emerged as a significant predictor. This unexpected finding is discussed in more depth under "Methodological Priming Effects" below.

Objective and subjective measures of the child's NDD severity did not hold up as predictors of emotional distress. This notion is supported by past research, in which characteristics of the child's DD, epilepsy, or CP had no bearing on parents' distress or diagnosis resolution when accounting for other predictors (Minnes, Perry & Weiss 2015; Pianta et al. 1996). Rather, as these and other studies have postulated, experiences of distress and mood disturbance are influenced directly by coping mechanisms (e.g., reframing, positive reappraisal, cognitive restructuring) and coping efficacy. When choice of coping strategy is misaligned with the needs of the situation, or an individual's coping reserves are completely overloaded, psychological wellbeing can be compromised.

Overall, the affective outcomes we examined seem to be impervious to the NDD appraisals and other caregiver/child attributes that we assessed in this study, in contrast with data from past studies (e.g., Gatzoyia et al. 2014; Hagger & Orbell 2003). It could be that other dispositional or situational variables not evaluated here exert a greater influence over caregivers' emotional disturbances. Furthermore, there was relatively little variance and a strong positive skew in the distribution of self-reported depressive, anxious, and stress symptoms among participants. Only a small proportion of caregivers fell within the "abnormal" or "clinical" (moderate to severe) range of the DASS-21 scoring guide, which is inconsistent with the mass of previous research showing NDD caregivers' susceptibility to adverse mental health outcomes over the general population (e.g., Byrne et al. 2010; Miodrag et al. 2010; Hayes et al. 2013). (Note, however, that the DASS-21 is not intended as a diagnostic tool.) This highly skewed

distribution may have obscured any true predictive relationships between variables, and it is difficult to know whether our sample's emotional wellbeing is truly representative of that of the broader population of caregivers. Conversely, differences in study design, scales, and analytic approach may account for the absence of significant relationships between covariates and the DASS-21 variables.

Effects of COVID-19 on Respondents

By the time that study recruitment began in September 2020, the novel coronavirus (COVID-19) pandemic had disrupted daily life and healthcare service delivery for nearly six months. A considerable proportion of the families in our sample had endured a shelter-in-place order at some point since March 2020, and a sizable majority experienced total or partial interruption of therapies and other services for their children as a consequence. As a result of the pandemic, caregiving burden shifted for respondents such that most caregivers reported spending much more or a little more time performing caregiving tasks for their child than before COVID-19. Nearly half of participants were not financially affected by the pandemic, and of those that were, few characterized these hardships as serious (see **Tables 12 and 13**).

Aside from this one trend between anxiety and COVID-related caregiving change, the effects of the ongoing global pandemic did not appear to confound the key relationships under study in the logistic regression models. However, some caution should be exercised in interpreting findings from our study against the backdrop of a historic and monumental public health crisis. Our sample may not have captured caregivers most severely impacted by pandemic-related difficulties, especially with respect to financial stability and livelihood. It could be that priorities and competing demands for time and cognitive energy deterred these caregivers from completing the survey, resulting in a self-selection bias effect.

Time as a Predictor

Contrary to our hypotheses, neither temporal distance from initial clinical attention nor from return of ES results was associated with any of the four outcome variables. Furthermore, adding either time variable to the regression models failed to improve the models' Nagelkerke R^2 by more than 2% for any of the outcome variables. There are several possible explanations for the observed lack of association. On the one hand, families who are further from these mile markers have had more time to process and come to terms with the implications of their child's condition. However, that elapsed time may also invite opportunities for adverse events in the affected child or in the family more broadly, which could lead to setbacks or stalling in the adaptation process. It may therefore be true that there is no linear relationship between time and psychological outcomes in these families.

It is also worth noting that survey responses were heavily skewed toward recent ES results, with fewer caregivers representing greater elapsed time since ES was completed (see **Figure 3** under Results). This asymmetric distribution could reflect a self-selection bias among respondents, in which caregivers who went through the ES process longer ago were less inclined to take the survey due to poor memory or decreased feelings of personal relevance.

Methodological Priming Effects

Depression was significantly predicted by PAS/PUCHS randomized display order ($p \leq .01$) connoting a strong emotional priming or framing effect in which viewing the PAS second (directly before the DASS-21) was associated with lower depression ratings, holding all other variables constant. By reading statements about the ways that parenting a child with an NDD could be meaningful, caregivers seemed to experience a transient boost in mood that translated to fewer self-reported depressive symptoms on the DASS-21 directly following. This incidental

finding may carry important implications for future survey design, especially if using similar measurement scales. Investigators should consider employing a counterbalancing approach like the one in the current study as a means to test for the presence of similar order effects. Another consideration is to alternate positive and negative framing between sections within a scale to try to neutralize its overall affective charge. However, at minimum, this would require pilot testing and ideally validation and reliability analyses to affirm that any semantic changes maintain the integrity of the measure.

Study Limitations

There are several limitations in this study that merit discussion. The cross-sectional nature of this study does not allow for inferring causal relationships. The sample size fell short of our target, which likely rendered our analyses underpowered and less sensitive to relationships with smaller effect sizes. Even if we had attained our recruitment goal, the initial power analysis conducted for the study was powered to detect effect sizes (r^2) around .3 to .4 in regression models with only one key predictor variable. As such, our extensive regression models with up to eight key predictor variables may have obfuscated small effects for any single key variable with our final sample size of 182. Some of these effects may have otherwise been detectable with a larger sample. Although the regression models did reveal a handful of significant predictors among the variables we controlled for, only one key variable (emotional representation) hypothesized to predict adaptation, depression, stress, and anxiety emerged as statistically significant. Finally, although the IPQ-RA has been validated for use with ASD, no validation studies have yet to be conducted for other types of NDD, such as intellectual disability and global developmental delay. The PUCHS and PAS have not been validated for use in families with NDD, and this will be an important undertaking if these measures are to be deployed to this

population in future research. Despite these constraints, the study draws strength from its grounding in a solid theoretical framework that enabled conceptual harmonization between variables of interest, guided study design, and facilitated informed interpretation of study findings.

The research aims and findings are predicated on a general assumption that participants correctly recall their child's ES results. Because we relied on self-report measures in lieu of clinically abstracted data to protect respondent anonymity, it is conceivable that participants' reported ES results did not match those disclosed by their genetics team. Such discrepancies have been reported in previous studies, especially for individuals who receive a clinically uncertain result from genetic testing (Bonner 2017; Biesecker, Tibben & Vos 2019), though the evidence on accuracy of patient recall of ES results is mixed (Medendorp et al. 2020). We also did not ask about nor account for ES reanalysis, where the clinical classification of a variant can change over time, nor about multiple categories of findings present in a single report. In addition, comprehension of ES findings and confidence in recalling results were not assessed in the survey. With that said, prior research indicates that patients' interpretations of their genetic results are better predictors of risk perception, family communication practices, and behavioral outcomes than the result that is actually communicated to them (Bonner 2017; Klein, Biesecker & Turbitt 2019). Thus, the ES result label assigned by the testing laboratory and genetics care team, in the absence of the caregiver's nuanced interpretation, may be inadequate to ascertain which families need more support in navigating uncertainty and adapting to their child's condition.

As is the case with many similar research studies, our sample was demographically homogeneous. The majority of our participants were white, non-Hispanic or Latinx, female,

married, highly educated, financially well-resourced, and the biological parents to their children, despite the fact that the recruiting institutions serve a racially and socioeconomically diverse population within Baltimore. Interacting with the recruitment email and the electronic survey requires some degree of technological savviness, and the time demands associated with completing the survey may have discouraged invitees already strained for time and resources from participating. As a result, these findings may not be generalizable to other groups of caregivers of individuals with NDD.

The validated measures used in the survey varied in terminology and language to discuss illness. Some referred to "symptoms," others to "condition." Wording was left unaltered to preserve the integrity of the instrument, and because it performed well during pilot testing. However, responses to the free-response questions at the conclusion of the survey indicated that this inconsistency generated some confusion for respondents.

Practice Implications

Exome sequencing is rapidly gaining traction as a first-line genetic testing approach for neurodevelopmental disorders (Srivastava et al. 2019). Although the categories of results in ES are parallel to antecedent technologies like CMA, ES as a testing modality is important to explore because it may carry a greater weight of finality and signal a metaphorical "end of the road" or a diagnostic odyssey. ES is currently the most comprehensive method of genomic analysis readily available on a clinical basis (Blesson & Cohen 2019). As more patients with NDD pass through the clinical genomics pipeline and undergo diagnostic ES, genetic counselors who meet families should be poised and equipped to help families understand ES findings, integrate them meaningfully into their lives, and actively engage in appropriate coping. This

work will necessarily stem from an understanding of the factors that strengthen and weaken caregivers' adaptive processes.

Our study contributes to our understanding of families of children with NDD by identifying several trends toward associations between adaption, caregiver characteristics, and illness representations. The insights from our study can help genetic counselors and other healthcare professionals working with these families to personalize the information, resources, and psychoeducational methods they use to frame a clinical encounter. Notably, three of these are appraisals within the Transactional Model of Stress and Coping and thus potential targets for therapeutic intervention in the clinic. As illness representations are schematic in nature and often operate subconsciously (Leventhal et al. 1980; Bishop & Converse 1986), a skillful genetic counselor will first help enhance a caregiver's awareness of his or her own cognitive and emotional representations of the NDD. It may be beneficial for the genetic counselor to elicit the caregiver's perceptions of his or her child's differences during the pre-test session, and then revisit these observations at follow-up appointments to discern any changes.

A number of potential tactics and interventions can be considered for caregivers of children with NDD in the pre-ES testing meeting. For all families, genetic counselors should delve into the personal significance of a genetic diagnosis as part of the informed consent conversation for ES. Bearing in mind that ES yields a genetic cause for NDD in fewer than half of cases, an important piece of anticipatory guidance is to explore families' current causal beliefs about their child's NDD, and how expect they will respond to an unrevealing outcome. On the affective side, genetic counselors may also encourage caregivers to reflect on feelings related to their child's condition and use reframing techniques to relocate the emotional focus. Referral to

psychotherapy for the individual caregiver, the couple, or the family may be indicated if adverse feelings related to the child's NDD are persistent and psychically taxing.

Perceptions of personal control may be bolstered through deliberate assessment and conversation with caregivers that combines strengths-based and solution-focused techniques. The genetic counselor can use a progressive framework of questions, such as that outlined by White (2002): *externalizing* (determining how the problem has attempted to control the client's life), *landscape-of-action* (identifying times when the client feels he or she has control over the problem), *landscape-of-consciousness* (reflecting on how the client has actually solved problems and recognized his or her ability to do so), and *future-oriented* (focusing on potential solutions). Through these questions, the counselor invites dialogue about the ways in which caregivers believe they can help their children navigate their condition, and jointly strategizes with them on means of boosting control and self-efficacy. As suggested by previous research in other medical settings, it may benefit caregivers to examine their beliefs around internal vs. external health locus of control, which has shown promise as a target for intervention with postpartum women (Moshki et al. 2013) and adults with chronic pain (Coughlin et al. 2000). Although both studies employed longer-term programs consisting of sessions spanning several weeks, similar principles may be adapted to a short-term genetic counseling format; this would require further evaluation through experimental designs.

Successful interventions have also been deployed to promote client empowerment,[4] a construct closely related to perceived personal control and a key outcome for genetic counseling (Yuen et al. 2019). Shearer and colleagues (2007) demonstrated that an empowerment

[4] Empowerment is defined as "a set of beliefs that enable a person from a family affected by a genetic condition to feel that they have some control over and hope for the future" (McAllister, Dunn & Todd 2011, cited in Yuen et al. 2019).

intervention delivered over the phone by nurses, which focused on goal attainment and solutions to health concerns, facilitated self-management of heart failure among diagnosed patients. Although there is recent evidence that the process of genetic counseling itself enhances empowerment (Ison et al. 2019), genetic counselors can maximize its benefits to families with NDD by tackling specific cognitive representations during the visit.

In the results disclosure visit and following sessions, genetic counselors should be attuned to how particular NDD representations differ across types of ES results and adjust their session goals accordingly. For example, knowing that families that receive a positive ES finding are prone to lower perceived treatment control can prompt the counselor to probe what "treatment" looks like to the child's caregivers. For some caregivers, outlining the wide range of treatment approaches may help broaden their views of what could be effective, and generate ideas for personalized resources that the genetic counselor can provide. This discussion could involve highlighting different treatment modalities (e.g., biomedical, behavioral, speech/ language) and settings (school, home) (Mire et al. 2017).

Conceptualizing uncertainty as nuanced and multi-faceted may help genetic counselors and other healthcare professionals to deepen their psychosocial work with families. Irrespective of the outcome of genetic testing, clinicians should assess and attend to the ways in which the lack of closure or uncertainty resolution impacts NDD caregivers' overall coping and functioning. Offering labels or categories for uncertainty, such as those presented in the PUCHS, can be empowering in expanding the language that caregivers have to discuss their experiences. If feasible within the clinical structure and workflow, families that receive non-diagnostic results from ES may warrant periodic follow-up from genetic counselors or other providers. Furthermore, genetic counselors can be instrumental in facilitating connections between their

patient families and support organizations, thereby reducing social support-related uncertainty and enhancing potential outcomes like life satisfaction and positive affect (Halstead et al. 2018).

For certain types of ES results, attention to specific domains of uncertainty may be warranted. As indicated by the current findings, caregivers receiving different kinds of results from ES diverge along uncertainty dimensions as well as in overall perceptions of uncertainty. For instance, families that receive VUS results from ES may be more susceptible to uncertainty regarding prognosis, reproductive risks, and social support than families receiving positive or negative results. A genetic counselor can keep on-hand an arsenal of resources designed to help these caregivers work through types of uncertainty that are most relevant and important to them. For example, if the client is unsure how to talk about the ES results with family members, the counselor could lead a role-play that allows the client to practice and gain confidence in delivering the information. If a caregiver is at a loss for where to seek support, the counselor may refer to a list of other families in the clinic with VUS results to make an introduction. Importantly, the more cognizant providers are of the varied sources and expressions of uncertainty, the better equipped they will be to provide individualized care to their families.

Areas for Future Research

Our study elucidated several potential relationships between caregivers' psychological state and the ways in which they view their child's NDD. However, as discussed above, the cross-sectional study design limited our analyses and the conclusions we can draw. A recent study with families with ASD queried parental perceived benefits of diagnostic genetic testing before and after return of results, but this was not a within-subjects design and thus uninformative about change in perception over time (Lucas 2020). Future projects with a more lenient timeline could collect longitudinal data at multiple time points from a similar study

population, capturing caregivers' pre-test expectations, hopes, and NDD perceptions to compare to post-test experiences over several follow-up interviews. Appraisal, coping, and adaptive processes are construed as dynamic and responsive, and this type of repeated measures design could allow for better isolation of the genetic result disclosure as a stressor that alters caregiver appraisals. It would also open up opportunities to understand what appraisals are formed *about the ES result itself*; this segment of the TMSC pathway was not evaluated in our study. Recent evidence points to the pivotal role of hope fulfillment in psychological adaptation as it relates to clinical genomic results (Griesemer et al. 2019), which could be examined alongside illness representations in better understanding NDD caregiver adaptation. This would necessitate a purposeful assessment of what aspects of hope are most pertinent to caregivers as they await ES results, perhaps through a qualitative design.

On the clinical side, little has been studied about provider communication during ES results disclosure. It is reasonable to suspect that the language and messaging used by healthcare professionals may influence caregivers' illness representations, feelings of uncertainty, and constructed meaning of genetic results. Although some ideas were proposed in the previous section, few targeted interventions have actually been tried and evaluated. Haakonsen Smith and colleagues (2018) demonstrated that a short-term, individualized coping effectiveness training was feasible and beneficial for parents of children with ASD within a genetic counseling setting. Assessment of novel counseling interventions through randomized controlled trials would assist in determining which types of therapeutic strategies, such as those informed by cognitive behavioral therapy (CBT), are efficacious and practicable for caregivers of individuals with NDD seen in the genetics clinic for ES testing.

Although this study measured multiple dimensions of time, including length of time since initial developmental concerns and length of time since first seeking clinical attention, we did not ask caregivers about genetic testing their child had prior to ES. Future research might explore whether similar predictors of adaptation surface between families who received ES as first-line genetic testing, and families who have had several uninformative rounds of testing before ES.

APPENDIX A: Glossary of Abbreviations

- ADHD: attention deficit hyperactivity disorder
- ASD: autism spectrum disorder(s)
- CBT: cognitive behavioral therapy
- CDC: Centers for Disease Control and Prevention
- CMA: chromosome microarray analysis
- CP: cerebral palsy
- DASS-21: Depression Anxiety Stress Scale—21 Item
- DBD: developmental brain dysfunction
- DD: developmental delay *or* disability
- ES: exome sequencing
- GDD: global developmental delay
- GS: genome sequencing
- ID: intellectual disability
- IPQ: Illness Perception Questionnaire
- IPQ-R(A): Revised Illness Perception Questionnaire (for Autism)
- JHM: Johns Hopkins Medicine
- KKI: Kennedy Krieger Institute
- NDD: neurodevelopmental disorder(s)
- PAS: Psychological Adaptation Scale
- PUCHS: Parental Uncertainty about a Child's Health Scale
- SRMIR: Self-Regulatory Model of Illness Representation
- TMSC: Transactional Model of Stress and Coping
- VUS: variant(s) of uncertain (*or* unknown) significance
- WES: whole exome sequencing

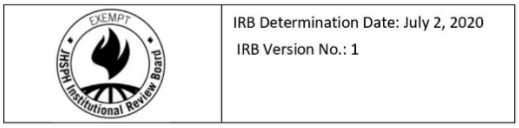
APPENDIX B: Variable Dichotomization Scheme for Logistic Regression Analysis

Table 1. Variable dichotomization scheme for logistic regressions outcome variables [$N = 182$]

Outcome Variable (Scale)	Cut-point Determination	Scale Range	Cut-point Value	Low (*N*)	High (*N*)
Adaptation (PAS)	Mean	0 – 20	3.75	87	96
Depression (DASS-21)	Scale scoring guide†	0 – 42	9	131	52
Anxiety (DASS-21)	Scale scoring guide†	0 – 42	7	142	41
Stress (DASS-21)	Scale scoring guide†	0 – 42	14	113	70
Weighted uncertainty (PUCHS)	Median	0 – 4	1.51	91	91

† Refer to Lovibond & Lovibond (1995).

APPENDIX C: Informed Consent / Study Information Sheet



PI: Debra Roter
Study title: Influence of diagnostic and non-diagnostic exome results on caregivers' representations of neurodevelopmental disorders
JHSPH IRB #12189
PI Version No. 5: June 22, 2020

APPENDIX C: Informed Consent Document

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH

Principal Investigator: Debra Roter, DrPH
Study Title: Influence of diagnostic and non-diagnostic exome results on caregivers' illness representation of neurodevelopmental disorders
IRB No.: IRB00012189
Sponsor/Supporter/Funded By: National Human Genome Research Institute, National Institutes of Health
PI Version Date: Version 5 / June 22, 2020

Purpose of the study: We are interested in learning about what it has been like for you to parent a child with a neurodevelopmental disorder. We also want to learn about how you view your child's condition. We would also like your thoughts about your child's genetic testing. We hope that this study will help guide future research and clinical practice to support other caregivers like yourself.

Why you may qualify: We ask you to join our study because your child had genetic testing done at Johns Hopkins Medicine (JHM) or Kennedy Krieger Institute (KKI). The name of the genetic test that your child had is *exome sequencing.* If you are a caregiver to a child or adult with a neurodevelopmental disorder who has had this test, you may choose to take part in this study. Neurodevelopmental disorders include, but are not limited to:

- Autism, autism spectrum disorder (ASD) including Asperger syndrome
- Developmental delay (DD), global developmental delay (GDD)
- Intellectual disability (ID), cognitive disability
- Cerebral palsy (CP)
- Movement disorder
- Epilepsy, seizure disorder

Your child may have several of these conditions. He or she may also have other developmental or behavioral differences.

You do not have to join. It is your choice. There will be no penalty if you decide not to join.

PI: Debra Roter
Study title: Influence of diagnostic and non-diagnostic exome results on caregivers' representations of neurodevelopmental disorders
JHSPH IRB #12189
PI Version No. 5: June 22, 2020

Joining the study: If you say yes, we will ask you to fill out a survey online that should take 15-25 minutes. We will start by asking a few basic questions about you to make sure that you are a good match for the study.

If you are a good match for the study, we will ask you questions about:

- What it has been like to care for a child or adult with a neurodevelopmental disorder
- The people that make up your family
- Your child's skills
- Your child's genetic testing process
- How you view your child's condition
- How your child's condition has impacted your life
- Your mood

Your answers will be anonymous. The survey does not ask any questions that would tell us about your identity or your child's identity.

Potential risks or discomforts: There is no risk of physical harm to you in this study. However, you may get tired or bored as you complete the survey. You may also become sad, anxious, uncomfortable, or frustrated when answering some of the questions.

Protecting your privacy: There is a small risk that someone outside the study will see your answers. We will do our best to keep your responses safe. We will give each survey an ID number instead of keeping your name or email. We will collect and store survey answers through a secure online system.

If your answers to a question include any names or information about other people or places, those names will be removed from the data file. This way, they cannot be connected to you.

A separate file will be used for your email address if you want to receive a gift card. This fill will have a password. This way, your email cannot be connected to your survey answers. After the gift cards have been sent out, we will destroy the file that contains your email address.

When we share survey answers with other researchers, we will ask them to use the same protections.

Benefits of participating: We do not expect that you or your child will personally benefit from the study. Your family will not receive any additional treatment or clinical care as part of the study.

However, it is possible that you will receive some benefit from thinking about the questions in the survey. Even if you do not benefit directly from the study, your answers will help us learn more about caregivers of people with neurodevelopmental differences. We hope this knowledge will improve future genetics services and care for families like yours.

Sharing results: We will share the results of the study with your child's clinic and with others who are interested in improving genetics services.

IRB Determination Date: July 2, 2020
IRB Version No.: 1

PI: Debra Roter
Study title: Influence of diagnostic and non-diagnostic exome results on caregivers' representations of neurodevelopmental disorders
JHSPH IRB #12189
PI Version No. 5: June 22, 2020

Payment: You have the option of providing your email address to receive a $5 Amazon gift card. If you choose to provide your email, it will not be linked to your survey response.

Other protections: Your study responses are protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you make yourself about your study information are not protected.

Study contacts: This study has been reviewed by an Institutional Review Board (IRB), a group of people including scientists and community people that reviews human research studies. The IRB can help you if you have questions about your rights as a research participant or if you have other questions, concerns or complaints about this research study. You may contact the IRB at 410-955-3193 or jhsph.irboffice@jhu.edu.

Please reach out to these points of contact if you have questions or concerns:

Amelia Mulford, BA
Student Investigator / Associate Investigator
JHU/NIH Genetic Counseling Training Program
Baltimore, MD
Email: amelia.mulford@nih.gov

Lori Erby, ScM, PhD
Primary Associate Investigator
National Human Genome Research Institute
Bethesda, MD
Phone: 301-443-2635
Email: lori.erby@nih.gov

Debra Roter, DrPH
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Johns Hopkins Bloomberg School of Public Health IRB
Phone: 410-955-3193
Toll free: 1-888-262-3242
Email: jhsph.irboffice@jhu.edu

Clicking "I Accept" and proceeding to the rest of the study means that you have reviewed the information in this form, you have had a chance to ask questions, and you agree to join the study. You will not give up any legal rights by clicking "I Accept."

I Accept I Do Not Accept

APPENDIX D: Recruitment Materials

IRB Determination Date: July 2, 2020
IRB Version No.: 1

PI: Debra Roter
Study title: Influence of diagnostic and non-diagnostic exome results on caregivers' representations of neurodevelopmental disorders
JHSPH IRB #12189
PI Version No. 5: June 11, 2020

APPENDIX D: Recruitment Templates

Email

Subject line: Invitation for research study about genetic testing

Dear [Caregiver Name],

We are reaching out from your child's genetics care team at [Kennedy Krieger Institute or Johns Hopkins Medicine] to invite you to participate in a survey-based research study. This study is being conducted as part of a graduate student research project. You're invited to join this study because your child previously had a clinical genetic test called **exome sequencing** (or **exome testing**). This test looked at all of the known genes that might be related to their developmental differences.

The purpose of the study is to learn about how you view your child's disorder, the positive and challenging aspects of parenting your child, and your experience with clinical genetic testing.

If you agree to participate in this research, you will be asked to complete an anonymous online survey that will take 15-20 minutes. Your survey response will not be linked to any identifying information about you or your child. At the end of the survey, you will have the option of providing your email address to receive a gift card as a token of appreciation for your time.

If you would like to learn more about the study and survey, please click on the link below:

[Survey Hyperlink]

If you would like to opt out of future emails about this research study, please reply to this email address (MulfordA@kennedykrieger.org) with the subject line **Opt Out**.

Thank you for your time. Please email MulfordA@kennedykrieger.org if you have any questions about this research study.

Sincerely,

Julie Cohen, ScM, CGC
Genetic Counselor
Kennedy Krieger Institute
Johns Hopkins Bloomberg School of Public Health

or

Weiyi Mu, ScM, CGC
Genetic Counselor
Johns Hopkins Medicine

PI: Debra Roter
Study title: Influence of diagnostic and non-diagnostic exome results on caregivers' representations of neurodevelopmental disorders
JHSPH IRB #12189
PI Version No. 5: June 11, 2020

JHSPH IRB #12189

Physical Letter

Dear [Caregiver Name],

We are reaching out from your child's genetics care team at [Kennedy Krieger Institute or Johns Hopkins Hospital] to invite you to participate in a survey-based research study. You're invited to join this study because your child previously had a genetic test called **exome sequencing** (or **exome testing**). This test looked at all of the known genes that might be related to their developmental differences.

The purpose of the study is to learn about how you view your child's disorder, the positive and challenging aspects of parenting your child, and your experience with clinical genetic testing.

If you agree to participate in this research, you will be asked to complete an anonymous online survey that will take 15-20 minutes. Your survey response will not be linked to any identifying information about you or your child. At the end of the survey, you will have the option of providing your email address to receive a gift card as a token of appreciation for your time.

If you are interested in filling out the survey, please type the following URL into your web browser:

[Survey Link]

Thank you for your time. Please email MulfordA@kennedykrieger.org if you have any questions about this research study.

Sincerely,

Julie Cohen, ScM, CGC Genetic Counselor Kennedy Krieger Institute	**or**	Weiyi Mu, ScM, CGC Genetic Counselor Johns Hopkins Medicine

JHSPH IRB #12189

APPENDIX E: Survey Instrument

Before we begin, we have a few questions that will determine whether you are eligible to join this study.

1. Are you primary caregiver to an individual with a neurodevelopmental disorder? ***[Response required]***
    a. Yes
    b. No *
2. Is this individual still living? ***[Response required]***
    a. Yes
    b. No *
3. Are you 18 years or older? ***[Response required]***
    a. Yes
    b. No *
4. Were you invited to participate in this study by a genetics provider at Kennedy Krieger Institute or Johns Hopkins Medicine? ***[Response required]***
    a. Yes
    b. No *
5. To your knowledge, has anyone else in your household already completed this survey? ***[Response required]***
    a. Yes *
    b. No

*** indicates responses that would trigger the survey to exit and redirect respondent to "Ineligible" end page**

Thank you for taking part in this survey. Throughout the questions you will read, NDD stands for "neurodevelopmental disorder." This includes conditions such as autism spectrum disorder (ASD), intellectual disability (ID), developmental delay (DD), cerebral palsy (CP), movement disorders, and others.

You were invited to take this survey because your child had a genetic test called exome sequencing, or exome testing. This test looked at all of the known genes that might be related to their NDD. The test can tell if there are any changes in those genes that could explain your child's condition.

About Your Child and Your Family

First, we would like to learn a little more about your child and family.

1. How many children do you have with some kind of NDD? _____

2. How many children do you have who have had exome testing for an NDD? _____

If your answer to Question #2 was more than 1, please answer the following questions on this page and the rest of the survey for your oldest child who had exome testing.

3. Did you already receive results from your child's exome testing? ***[Response required]***
    a. Yes
    b. No *

*** indicates response that would trigger the survey to exit and redirect respondent to "Results Disclosure Pending" end page**

4. How old is your child currently? *If your child is under 1 year of age, please enter 0.*
   _____ years

5. What is your child's gender?
    a. Male
    b. Female
    c. Other

6. How old was your child when you first had concerns about their behavior or development?
   _____ years _____ months

7. How old was your child when you sought out a behavioral or medical specialist about your concerns for your child's development? This may have been a pediatrician, early intervention specialist, neurologist, psychologist, or other provider. *If your child was under 1 year of age, please enter 0.*
   _____ years

8. Has a provider given you a diagnosis for your child's neurodevelopmental differences?
    a. Yes
    b. No
    c. I'm not sure

9. Do you feel that you are still searching for an explanation for your child's neurodevelopmental differences?
    a. Yes
    b. No

10. As far as you know, does your child have other family members with a known/diagnosed NDD? This includes your child's parents, siblings, nieces/nephews, cousins, aunts/uncles, and grandparents.
    a. Yes
    b. No

11. What is your relationship to your child?
    a. Biological parent
    b. Adoptive parent
    c. Foster parent
    d. Grandparent
    e. Stepparent
    f. Other (Please indicate: _____)

12. Does your child live at home with you?
    a. Yes, all the time
    b. Yes, part of the time
    c. No

13. How long have you been in the caregiving role for your child?
    a. His/her whole life
    b. Most of his/her life
    c. About half of his/her life
    d. Less than half of his/her life

14. Do you have a partner in providing care for your child?
    a. Yes, all the time
    b. Yes, part of the time
    c. No

About Your Child's Genetic Testing for NDD

15. How old was your child when you received results from exome testing? *If your child was under 1 year of age, please enter 0.*
    a. _____ years
    b. I don't know how old my child was

16. How much do you feel the exome findings explain your child's neurodevelopmental differences?
    a. Not at all
    b. A little
    c. Partly
    d. Mostly
    e. Completely

    Please explain your response to Q16 above:
    _____

17. What was the outcome of exome testing in your child?
    a. Positive (abnormal): the test found a gene change that is the cause of my child's NDD
    b. Negative (normal): the test did not find any gene changes related to my child's NDD
    c. Variant of uncertain significance (VUS) (inconclusive): the test found a change in one of my child's genes, but it is unclear whether this change is related to my child's NDD
    d. I'm not sure

18. Where did you see the doctor who ordered your child's genetic testing?
    a. Kennedy Krieger Institute
    b. Johns Hopkins Medicine
    c. I'm not sure

About Your Child's NDD

Next, please check the boxes below that describe problems that your child experiences. Check as many as apply to your child.

[ ] Autism / autism spectrum disorder
[ ] Intellectual disability
[ ] Developmental delay
[ ] Cerebral palsy
[ ] Movement disorder
[ ] Epilepsy / seizures
[ ] Birth defects
[ ] Other neurological problem
Please describe: _____

Please check the boxes below that describe tasks, skills that your child needs help with. Check as many apply to your child. This is to help us better understand your child's functioning with his/her NDD.

[ ] Moving around at home, school and/or community
[ ] Using his/her hands and arms to do the things he/she wants to do
[ ] Performing functions such as feeding/eating
[ ] Toileting
[ ] Dressing or undressing self
[ ] Sleeping each night
[ ] Seeing
[ ] Hearing
[ ] Understanding other people
[ ] Telling people what he/she wants
[ ] Behaving in an appropriate manner
[ ] Regulating his/her mood
[ ] Managing his/her pain
[ ] Learning new things
[ ] Remembering things they know
[ ] Getting along with other children
[ ] Getting along with adults
[ ] Participating in activities at home
[ ] Participating in activities at school or in the community

How serious is your child's condition compared with other children with an NDD?

a. Much <u>less</u> severe than other children with an NDD
b. Somewhat <u>less</u> severe than other children with an NDD
c. No more or less severe than other children with an NDD
d. Somewhat <u>more</u> severe than other children with an NDD
e. Much <u>more</u> severe than other children with an NDD

Next, we are interested in your own personal views of how you now see your child's condition. Please tell us how much you agree or disagree with the following statements about your child's condition by clicking the appropriate button for each statement.

	Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
1. My child's condition will last a short time.					
2. My child's condition is likely to be permanent rather than temporary.					
3. My child's condition will last for a long time.					
4. My child's condition will pass quickly.					
5. I expect my child to have this condition for the rest of his/her life.					
6. My child's condition is a serious condition.					
7. My child's condition has major consequences on my life.					
8. My child's condition does not have much effect on my life.					
9. My child's condition strongly affects the way others see me.					
10. My child's condition has serious financial consequences.					
11. My child's condition causes difficulties for those who are close to me.					
12. There is a lot I can do to control my child's symptoms.					
13. What I do can determine whether my child's condition gets better or worse.					
14. The course of my child's condition depends on me.					
15. Nothing I do will affect my child's condition.					
16. I have the power to influence my child's condition.					
17. My actions will have no effect on the outcome of my child's condition.					
18. My child's condition will improve in time.					
19. There is very little that can be done to improve my child's condition.					
20. My child's treatment will be effective in curing his/her condition.					
21. The negative effects of my child's condition can be prevented (avoided) by his/her treatment.					

22. My child's treatment can control his/her condition.					
23. There is nothing that can help my child's condition.					
24. The symptoms of my child's condition are puzzling to me.					
25. My child's condition is a mystery to me.					
26. I don't understand my child's condition.					
27. My child's condition doesn't make sense to me.					
28. I have a clear picture or understanding of my child's condition.					
29. The symptoms of my child's condition change a great deal from day to day.					
30. My child's symptoms come and go in cycles.					
31. My child's condition is very unpredictable.					
32. My child goes through cycles in which his/her condition gets better and worse.					
33. I get depressed when I think about my child's condition.					
34. When I think about my child's condition, I get upset.					
35. My child's condition makes me feel angry.					
36. My child's condition does not worry me.					
37. That my child has his/her condition makes me feel anxious.					
38. My child's condition makes me feel afraid.					

We are interested in what you consider may have been the cause of your child's condition. As people are very different, there is no correct answer for this question. We are most interested in your own views about the factors that caused your child's condition rather than what others including doctors or family may have suggested to you. Below is a list of possible causes for your child's condition. Please indicate how much you agree or disagree that they were causes for you by ticking the appropriate box.

	Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
Stress or worry					
Genetics / heredity					
A germ or virus					
Vaccines					
My child's diet or eating habits					
Chance or bad luck					
Poor medical care in my child's past					
Pollution in the environment					
My own behavior					
God's will					
Medical error					
Accident or injury					
My child's aging					
Deterioration of my child's immune system					
Pregnancy complication or birth injury					
Head trauma					
Early childhood illness					
Antibiotic or medication taken by my child					

On the lines below, please list in rank-order the 3 most important factors that you now believe caused your child's condition. You may use any of the items from the list above, or you may have additional ideas of your own.

The most important causes for me:
1. _____
2. _____
3. _____

Next, please think about how being a caregiver to a person with an NDD has impacted your life. Please click the button for how much you agree or disagree with the following statements.

Being a caregiver of an individual with an NDD has…

	Not At All	A Little Bit	Some-what	Quite a Bit	Very Much
1. …helped me accept the way things work out.					
2. …helped me learn to deal better with uncertainty.					
3. …taught me how to adjust to things I cannot change.					
4. …helped me take things as they come.					
5. …helped me to look at things in a more positive way.					
6. …helped me learn to handle difficult times.					
7. …helped me become more comfortable with who I am.					
8. …helped me become a stronger person.					
9. …helped me feel better about my ability to handle problems.					
10. …helped me become a better person.					
11. …helped me know who I can count on in times of trouble.					
12. …makes me more willing to help others.					
13. …helped relationships become more meaningful.					
14. …helped me become closer to people I care about.					
15. …helped me become more aware of the love and support available from other people.					
16. …helped me learn my life is more meaningful.					
17. …given me a greater appreciation for life.					
18. …helped me develop a deeper sense of purpose in life.					
19. …helped me feel peaceful.					
20. …helped me find strength in my faith or spiritual beliefs.					

Next, we'd like to hear about your experience with uncertainty related to your child's condition.

In Part A, please mark how much you agree with each statement by clicking the corresponding button. In Part B, please mark how important each type of certainty is to you by clicking the corresponding button.

PART A: Having a genetic diagnosis or not having a genetic diagnosis for my child's condition leaves me…

	Strongly Disagree	Disagree	Unsure	Agree	Strongly Agree
1A: …with no clear understanding of my child's limitations					
2A: …unsure how to think about my child's condition					
3A: …unsure of whether my child is expected to have a normal lifespan					
4A: …anticipating my child may do better than anyone has anticipated					
5A: …insufficiently prepared to participate in treatment decisions for my child					
6A: …unsure where to go for treatment of my child's condition					
7A: …lacking information to make decisions about having more children					
8A: …unsure what to tell relatives about risks to their children					
9A: …unprepared to inform my children about risks to their children					
10A: …ill-prepared to make decisions for my family not knowing what the future may hold for my child					
11A: …less able to address my family's concerns about my child					
12A: …struggling to find parents in a similar situation					
13A: …without support from parents going through similar experiences					
14A: …uncertain about the meaning of my child's life					
15A: …questioning the purpose of my child's life					

PART B: Please rank how **important** each is to you:

	Unimportant	Somewhat unimportant	Neutral	Somewhat important	Important
1B: Having a clear understanding of my child's limitations					
2B: Having a background against which to think about my child's condition					
3B: Being sure that my child is expected to have a normal lifespan					
4B: Anticipating that my child may do better than has predicted					
5B: Being prepared to participate in treatment decisions for my child					
6B: Knowing where to go for treatment of my child's condition					
7B: Having information to make decisions about having more children					
8B: Knowing what to tell relatives about risks to their children					
9B: Being prepared to inform my children about risks to their children					
10B: Being able to make decisions for my family not knowing what the future may hold					
11B: Addressing my family's concerns about my child					
12B: Finding parents in a similar situation					
13B: Having support from parents going through similar experiences					
14B: Having clarity about the meaning of my child's life					
15B: Understanding the purpose of my child's life					

Next, we have a few questions about how you've been feeling recently. Please read each statement and click the number 0, 1, 2 or 3, which indicates how much the statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:
0 -- Did not apply to me at all
1 -- Applied to me to some degree, or some of the time
2 -- Applied to me to a considerable degree or a good part of time
3 -- Applied to me very much or most of the time

	Not at all			Most of the time
1. I found it hard to wind down.	0	1	2	3
2. I was aware of dryness of my mouth.	0	1	2	3
3. I couldn't seem to experience any positive feeling at all.	0	1	2	3
4. I experienced breathing difficulty (e.g. excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5. I found it difficult to work up the initiative to do things.	0	1	2	3
6. I tended to overreact to situations.	0	1	2	3
7. I experienced trembling (e.g. in the hands).	0	1	2	3
8. I felt that I was using a lot of nervous energy.	0	1	2	3
9. I was worried about situations in which I might panic and make a fool of myself.	0	1	2	3
10. I felt that I had nothing to look forward to.	0	1	2	3
11. I found myself getting agitated.	0	1	2	3
12. I found it difficult to relax.	0	1	2	3
13. I felt down-hearted and blue.	0	1	2	3
14. I was intolerant of anything that kept me from getting on with what I was doing.	0	1	2	3
15. I felt I was close to panic.	0	1	2	3
16. I was unable to become enthusiastic about anything.	0	1	2	3
17. I felt I wasn't worth much as a person.	0	1	2	3
18. I felt that I was rather touchy.	0	1	2	3

19. I was aware of the action of my heart in the absence of physical exertion (e.g. sense of heart rate increase, heart missing a beat).	0	1	2	3
20. I felt scared without any good reason.	0	1	2	3
21. I felt that life was meaningless.	0	1	2	3

Next, we'd like to learn a little more about you.

1. What is your current age? _____

2. Which of the following best describes how you think of yourself?
    a. Male
    b. Female
    c. Other

3. What is your race? Check all that apply.
    a. American Indian/Alaska Native
    b. Asian
    c. Black/African American
    d. Native Hawaiian or Other Pacific Islander
    e. White
    f. Other

4. What is your ethnicity?
    a. Hispanic/Latinx
    b. Non-Hispanic/Latinx

5. What is your marital status?
    a. Married
    b. Divorced
    c. Widowed
    d. Single
    e. Partnered but not married
    f. Other

6. How would you describe your current employment status?
    a. Employed, full-time
    b. Employed, part-time
    c. Unemployed
    d. Retired
    e. Student
    f. Other

7. What is your highest level of education completed?
    a. Elementary or junior high school
    b. High school/GED
    c. Technical school

d. Some college
e. Completed college
f. Graduate degree

8. What is your annual household income?
    a. Under $30,000
    b. $30,000 - $50,000
    c. $50,001 - $70,000
    d. $70,001 - $100,000
    e. $100,001 - $250,000
    f. Above $250,000

The COVID-19 (coronavirus) outbreak has changed daily life for families across the country and around the world. We would like to hear a little about how the pandemic has affected your family. This will help us to better understand your answers to other questions in this survey.

1. At any point since March, have you been living under a shelter-in-place or shelter-at-home order?
    a. Yes
    b. No
    c. I don't know

[If "YES" to Q1] 2. Are you still under the shelter-in-place order?
    a. Yes
    b. No

[If "YES" to Q2] 3. For how many months have you been sheltering in place? _____

[If "NO" to Q3] 4. For how many months were you sheltering in place? _____

5. In thinking about the time before COVID-19 compared to now, how has your caregiving situation changed?
    a. I spend **much more** time performing activities related to caring for my child now than before COVID-19
    b. I spend **a little more** time performing activities related to caring for my child now than before COVID-19
    c. I spend the **same amount** of time performing activities related to caring for my child now as I did before COVID-19
    d. I spend **a little less** time performing activities related to caring for my child now than before COVID-19
    e. I spend **much less** time performing activities related to caring for my child now than before COVID-19

6. Have you had any interruption of therapies or other services for your child due to COVID-19?
    a. Yes, all services were interrupted
    b. Yes, some services were interrupted
    c. No, none of my child's services were interrupted
    d. Not applicable

7. Have you had financial difficulties due to COVID-19?
    a. Yes. We have experienced serious financial challenges.
    b. Yes. We have experienced some financial challenges that I would not consider to be serious.
    c. Yes. There have been minor negative effects on our financial situation.
    d. No. Our financial situation has not been affected by COVID-19.
    e. I don't know yet whether or not we will face financial challenges related to COVID-19.
    f. I prefer not to answer.

We will end by hearing from you about your overall experience. In your responses below, please be sure to not include any identifying information about your child.

1. In a few sentences, please share how exome testing has had a positive impact on your life, if at all.

2. Please share how exome testing has had a negative impact on your life, if at all.

3. Think back to when you decided for your child to have exome testing but hadn't received the results yet. What were your hopes and expectations for the testing?

4. Thinking about the impact of the COVID-19 pandemic on your family, how different do you imagine your responses to the survey questions would be if you had answered before the pandemic?
    a. Extremely different
    b. Very different
    c. Somewhat different
    d. Slightly different
    e. No different

5. Anything else you would like to share with us?

Thank you for taking the time to complete this survey. We appreciate you sharing your thoughts with us and helping us to better understand the experience of caregivers of children with neurodevelopmental disorders.

If you would like to receive a $5 Amazon gift card in exchange for your time, please click the link below. This will take you to an external page with a form, where you can enter your email address. *Your email address will not be associated with the current survey response in any way.*

Link

If you have any questions about information presented in this study, you can reach out to the researchers or contact the Johns Hopkins Bloomberg School of Public Health IRB Office.

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If you need to talk to someone about any feelings or questions that were brought up because of this study, please contact the research team or utilize the following resources:

National Alliance on Mental Illness Helpline - 1-800-950-NAMI (6264)
National Alliance on Mental Illness Crisis Text Line - Text NAMI to 741-741

If you would like to reach out and connect with other families of individuals with disabilities, you can find a list of support resources below:

- Understood (national): http://www.understood.org
- The Arc (regional): https://thearc.org/
- The League for People with Disabilities (Baltimore area): https://www.leagueforpeople.org/

APPENDIX F: Factor Loadings for PUCHS and PAS

Table 1. Factor loadings for the PUCHS

Weighted Item	Component of Uncertainty			
	Medical Management	Family/ Reproductive	Social	Existential
1. …with no clear understanding of my child's limitations.	.79	-.04	.02	.01
2. …unsure how to think about my child's condition.	.88	-.08	-.03	.03
3.* …unsure of whether my child is expected to have a normal lifespan.	.30	.07	.32	.05
4.* …anticipating my child may do better than anyone has anticipated.	.11	.04	.09	-.02
5. …insufficiently prepared to participate in treatment decisions for my child.	.43	.22	.01	.04
6. …unsure where to go for treatment of my child's condition.	.48	.15	.04	.08
7. …lacking information to make decisions about having more children.	.12	.44	-.09	.18
8. …unsure what to tell relatives about risks to their children.	-.10	.97	.01	-.01
9. …unprepared to inform my children about risks to their children.	-.01	.81	.05	-.03
10. …ill-prepared to make decisions for my family not knowing what the future might hold for my child.	.23	.37	.17	.16
11. …less able to address my family's concerns about my child.	.29	.54	.14	.03
12. …struggling to find parents in a similar situation.	-.03	-.02	.98	.02
13. …without support from parents going through similar experiences.	-.02	.01	.90	.08
14. …uncertain about the meaning of my child's life.	.05	.02	-.04	.94
15. …questioning the purpose of my child's life.	-.05	-.03	.09	.88

* Item excluded from scale following factor analysis

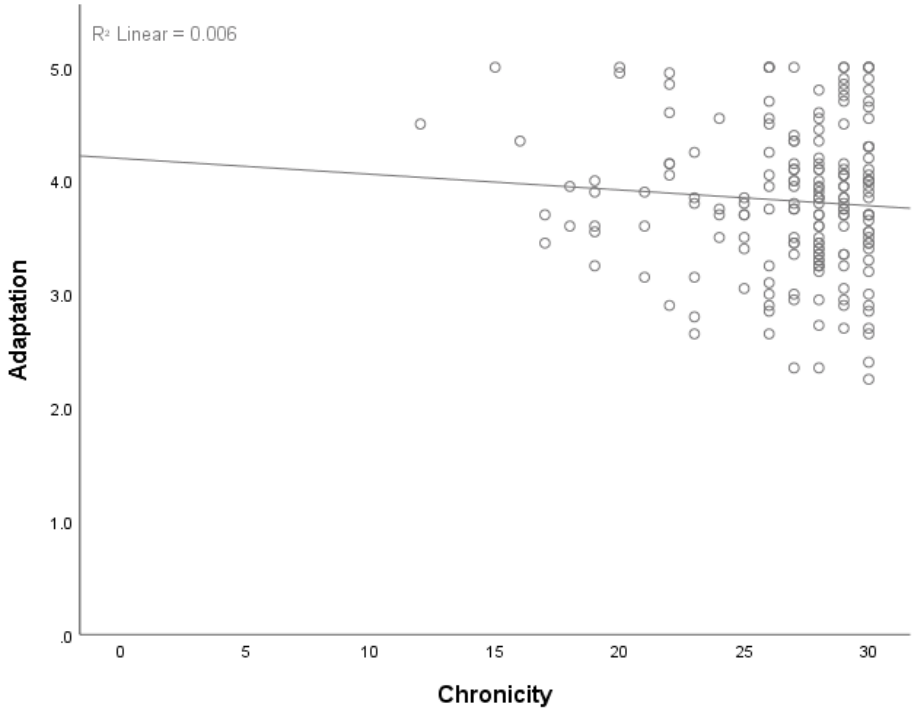
Note: Highlighted values indicate which factor (or component) the item is part of. Factor loadings represent factor analysis of the weighted uncertainty scores.

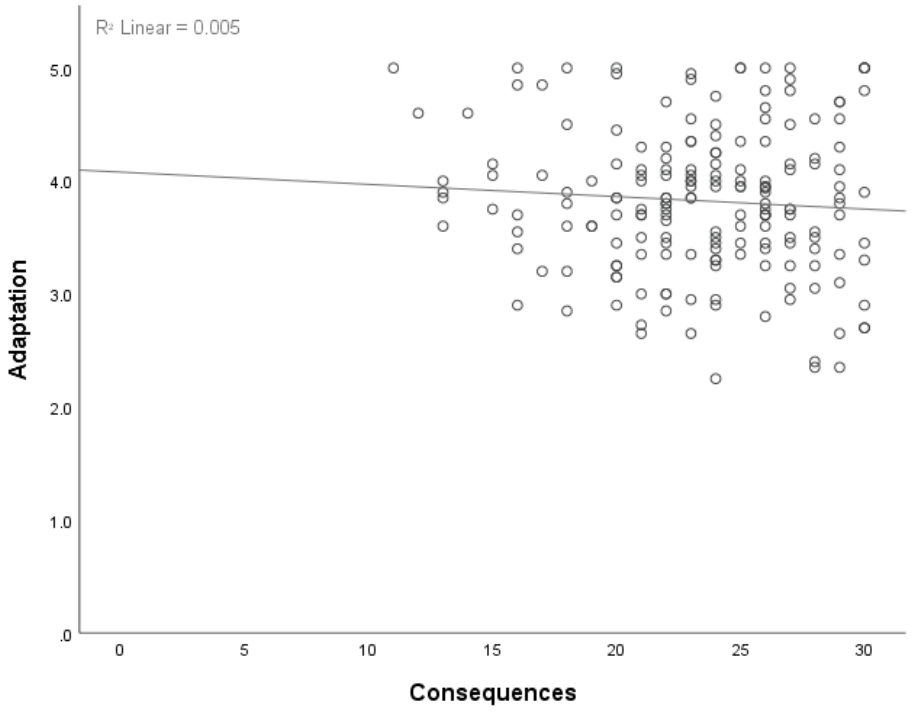
Table 2. Factor loadings for the PAS

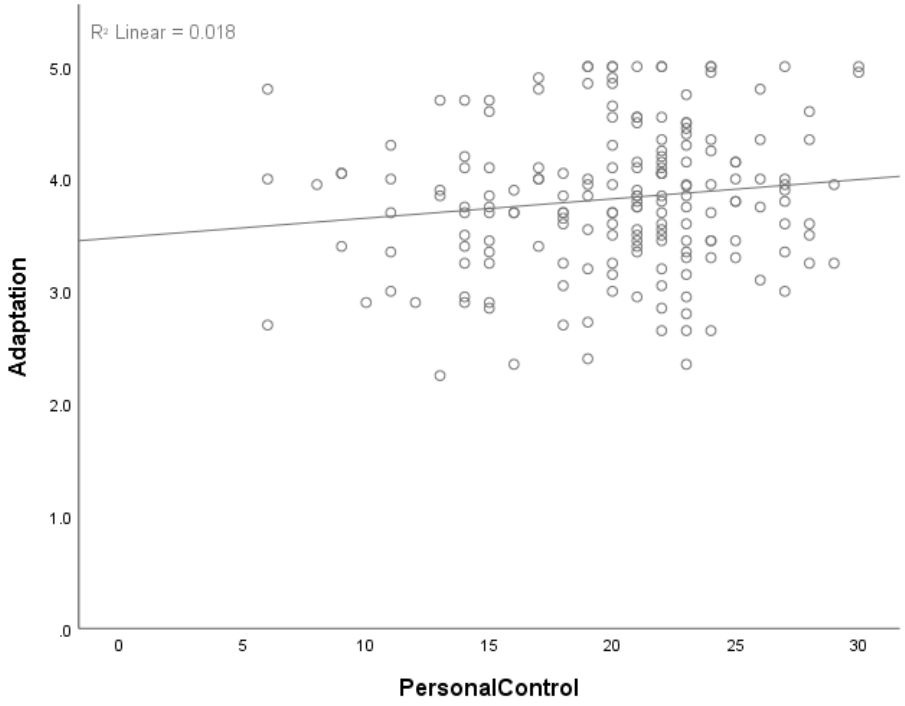
Item	Component of Psychological Adaptation			
	Coping efficacy	Self-esteem	Social integration	Spiritual wellbeing
1. …helped me accept the way things work out.	.63	.03	.12	-.14
2. …helped me learn to deal better with uncertainty.	.81	-.07	-.06	-.04
3. …taught me how to adjust for things I cannot change	.95	.03	-.10	.03
4. …helped me take things as they come.	.88	.07	-.00	-.01
5. …helped me to look at things in a more positive way.	.34	-.22	.03	-.30
6. …helped me learn to handle difficult times.	.40	-.34	.04	-.14
7. …helped me become more comfortable with who I am.	.26	-.28	.01	-.33
8. …helped me become a stronger person.	.01	-.73	.02	-.21
9. …helped me feel better about my ability to handle problems.	.11	-.76	.01	-.04
10. …helped me become a better person.	.02	-.58	.16	-.19
11. …helped me know who I can count on in times of trouble.	.19	-.27	.42	.21
12. …makes me more willing to help others.	.02	-.28	.45	-.05
13. …helped relationships become more meaningful.	-.05	-.00	.92	-.06
14. …helped me become closer to people I care about.	-.02	.18	.83	-.22
15. …helped me become more aware of the love and support available from other people.	.07	-.07	.62	-.05
16. …helped me learn my life is more meaningful.	.09	-.14	.05	-.73
17. …given me a greater appreciation for life.	.17	-.16	.08	-.58
18. …helped me develop a deeper sense of purpose in life.	.02	-.16	.02	-.72
19. …helped me feel peaceful.	.06	.05	.08	-.73
20. …helped me find strength in my faith or spiritual beliefs.	.06	.00	.12	-.53

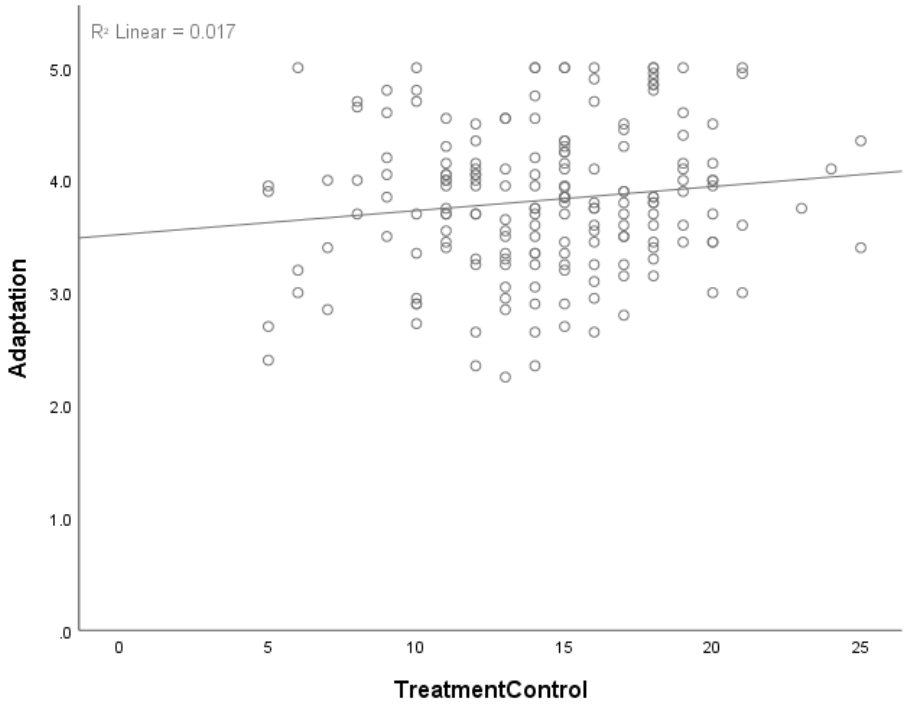
Note: Highlighted values indicate which factor (or component) the item is part of.

<u>APPENDIX G</u>: Scatterplots for Investigation of Linear Relationships Between Adaptation and Predictor Variables






R² Linear = 0.018
Adaptation
PersonalControl
5.0
4.0
3.0
2.0
1.0
.0
0
5
10
15
20
25
30


R² Linear = 0.017
Adaptation
TreatmentControl
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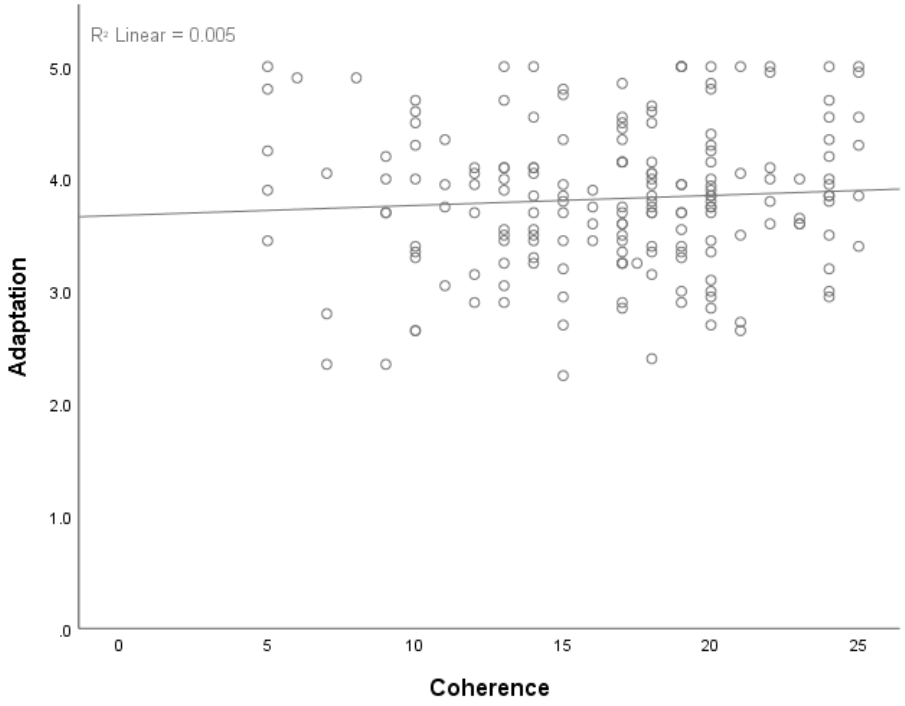
4.0
3.0
2.0
1.0
.0
0
5
10
15
20
25


R² Linear = 0.005
Adaptation
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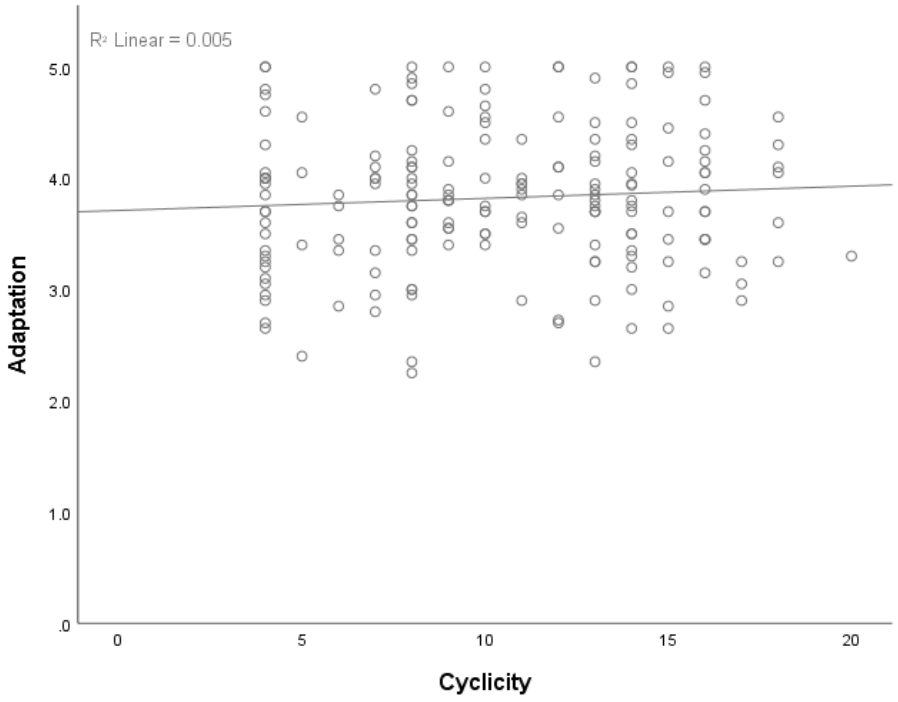
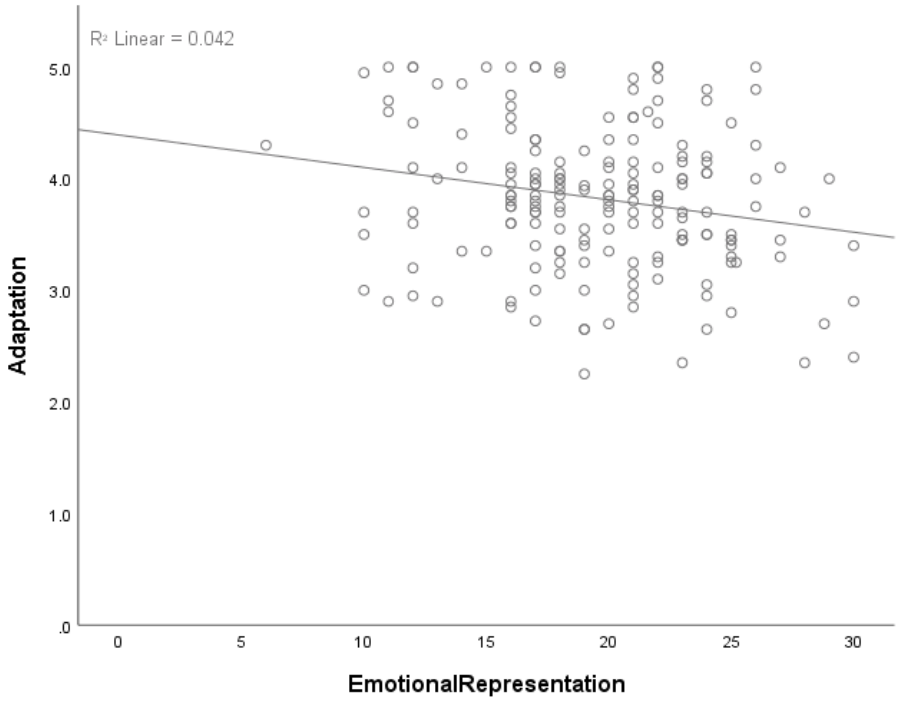
4.0
3.0
2.0
1.0
.0
0
5
10
15
20
25
Coherence


R² Linear = 0.005
Adaptation
5.0
4.0
3.0
2.0
1.0
.0
0
5
10
15
20
Cyclicity


R² Linear = 0.042
Adaptation
EmotionalRepresentation
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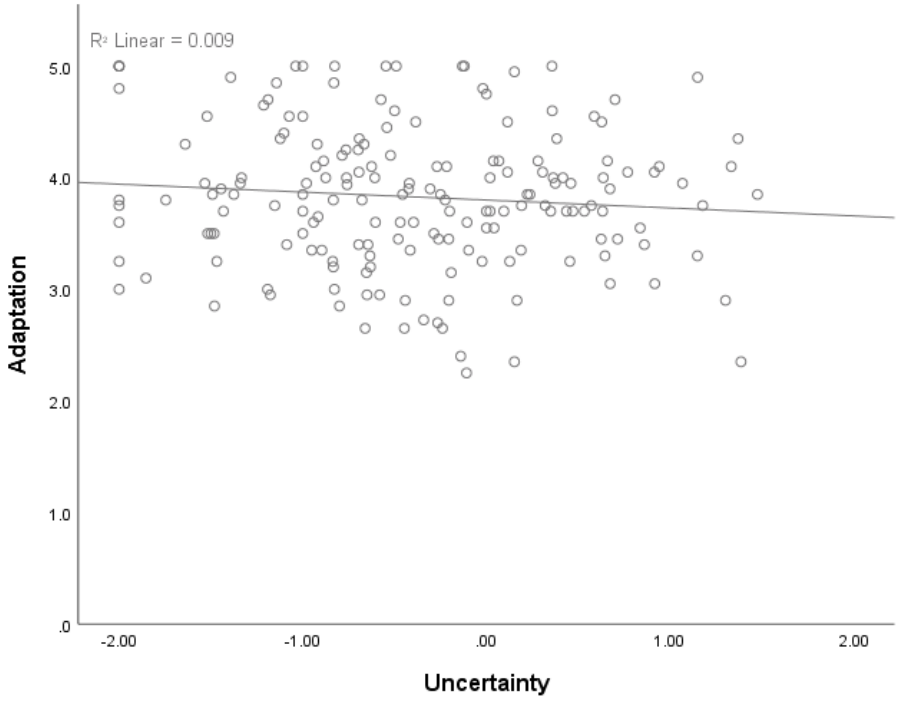
4.0
3.0
2.0
1.0
.0
0
5
10
15
20
25
30


R² Linear = 0.009
Adaptation
Uncertainty
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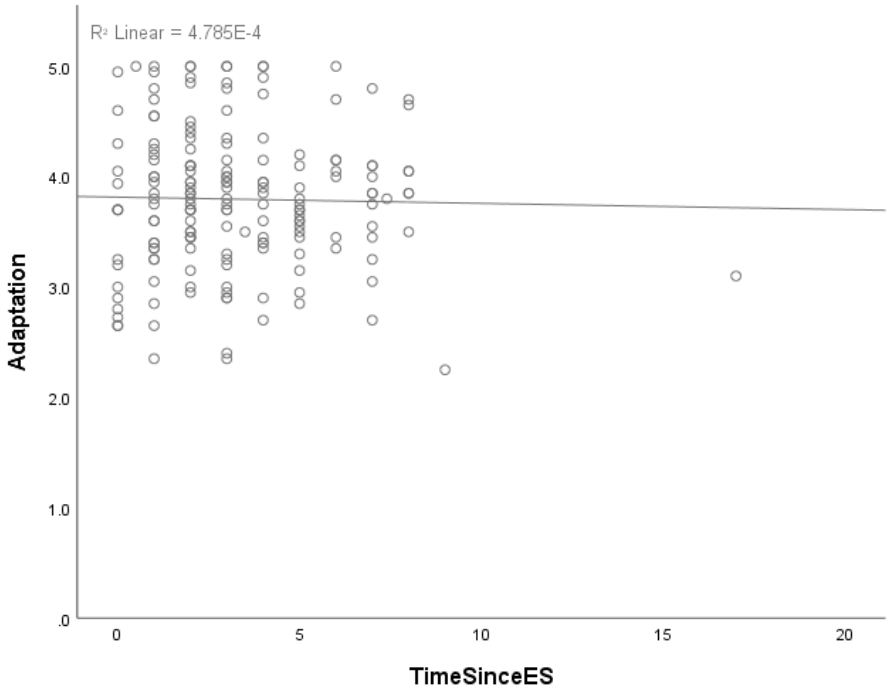
3.0
2.0
1.0
.0
-2.00
-1.00
.00
1.00
2.00


R² Linear = 4.785E-4
Adaptation
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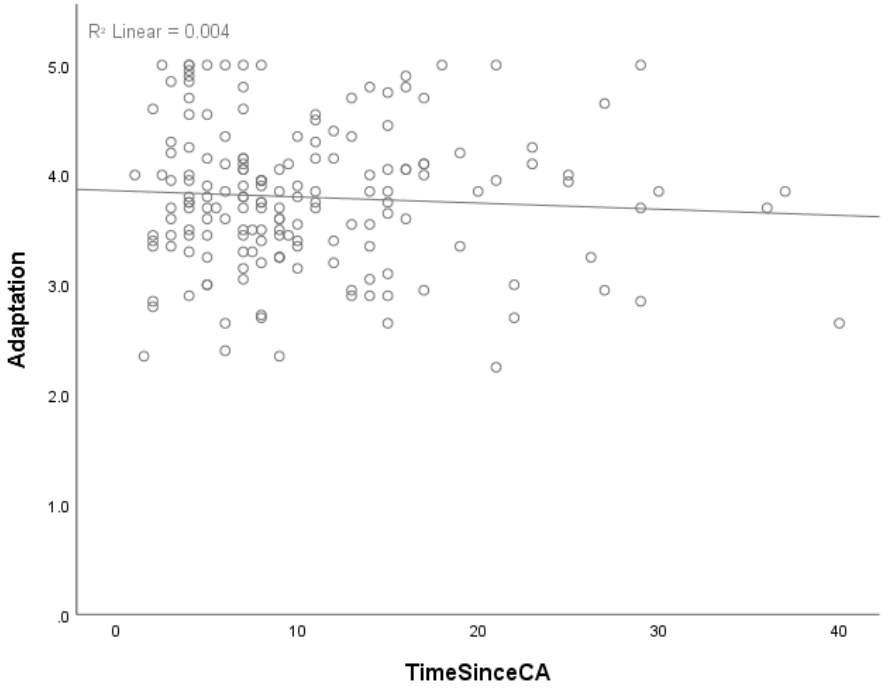
3.0
2.0
1.0
.0
0
5
10
15
20
TimeSinceES


R² Linear = 0.004
Adaptation
5.0
4.0
3.0
2.0
1.0
.0
0
10
20
30
40
TimeSinceCA

APPENDIX H: ROC Curves for Logistic Regression Models

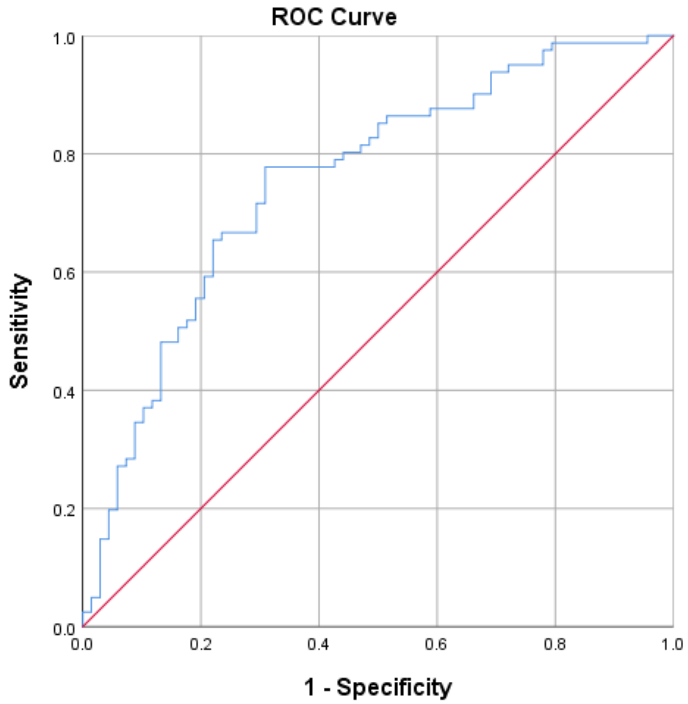


Figure 1. ROC curve for the logistic regression with adaptation as the dependent variable.

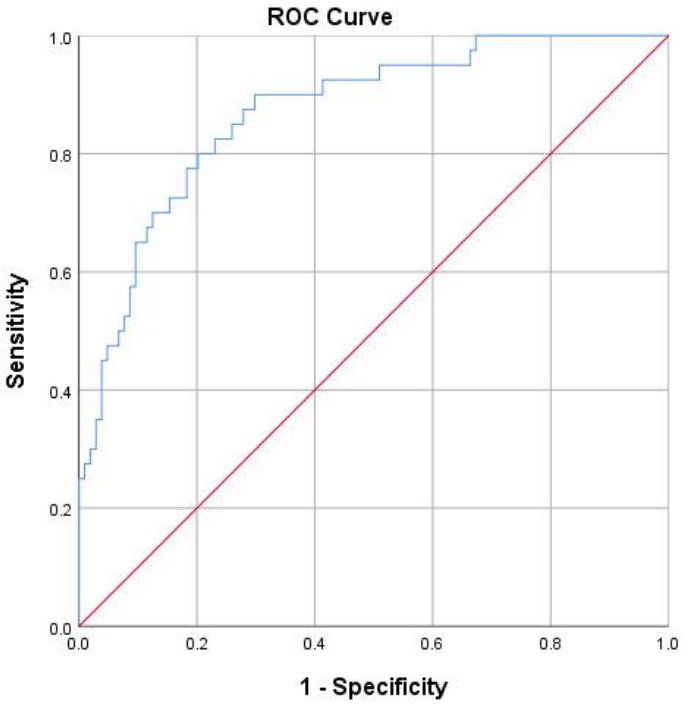


Figure 2. ROC curve for the logistic regression with depression as the dependent variable.

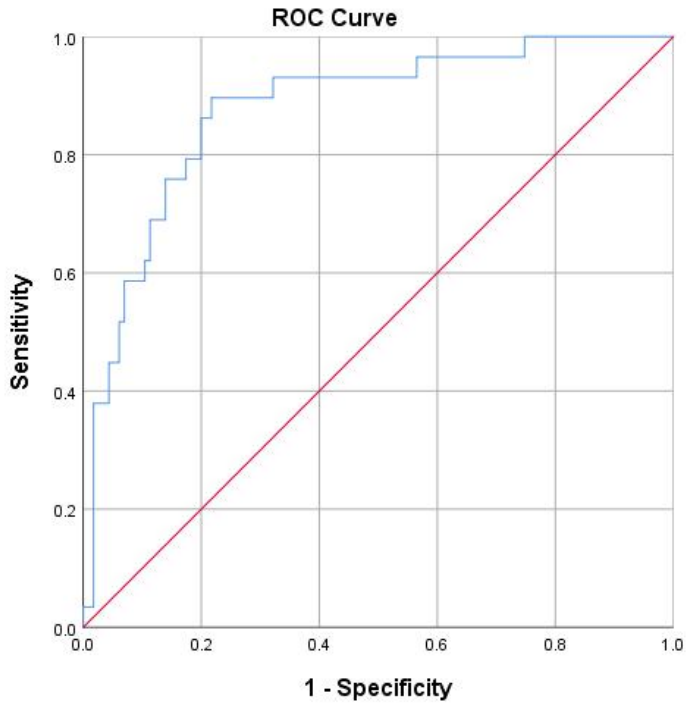


Figure 3. ROC curve for the logistic regression with anxiety as the dependent variable.

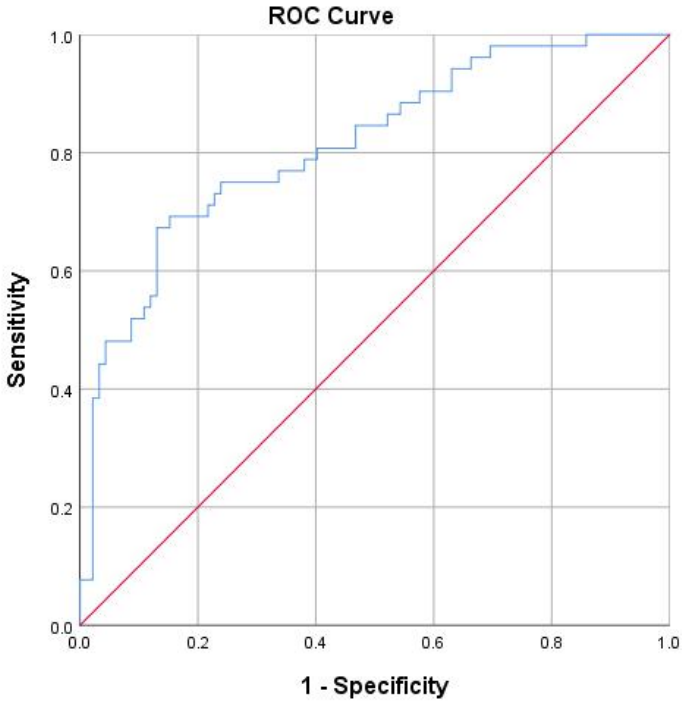


Figure 4. ROC curve for the logistic regression with stress as the dependent variable.

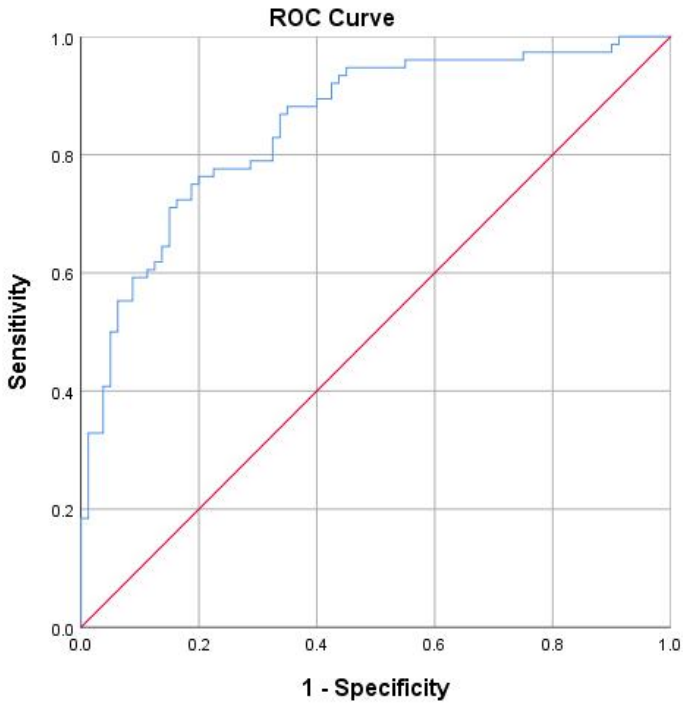


Figure 5. ROC curve for the logistic regression with weighted uncertainty as the dependent variable.

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EDUCATION & ACADEMIC ACHIEVEMENTS

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD — January 2021
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Lewis & Clark College, Portland, OR — May 2014
Bachelor of Arts, Psychology & Hispanic Studies, *magna cum laude*

Phi Beta Kappa Society	April 2014
Award for Academic Excellence in Hispanic Studies	April 2014
Psi Chi International Honor Society in Psychology	May 2011
Dean's List	Fall 2010 – Spring 2014
Lewis & Clark Overseas Program: Valparaíso, Chile	Fall 2012

PROFESSIONAL EXPERIENCE

Intramural Research Training Award Fellow — September 2018 – January 2021
National Human Genome Research Institute, Bethesda, MD

Program Assistant/Coordinator | Newborn Screening — September 2016 – July 2018
Genetic Alliance, Washington, DC

- Provided support to Baby's First Test, the nation's newborn screening clearinghouse, including website maintenance, partner outreach, call coordination, and resource center requests
- Curated content for BabysFirstTest.org, Spanish.BabysFirstTest.org, and monthly newsletter
- Assisted in rollout of social media campaigns for Newborn Screening Awareness Month, Spanish Saturdays, and others on Twitter/Facebook/Instagram via Hootsuite
- Led parent disease-specific education work groups as subcontractor to APHL NewSTEPs
- Crafted briefs, reports, and abstracts related to educational initiatives and Hispanic family engagement
- Networked and shared newborn screening educational materials at national conferences
- Aided in brainstorming, development, design, and content creation for the launch of Expecting Health, Genetic Alliance's maternal-child health program

Research Assistant I | Behavioral Neuroscience, Raber Lab — January – July 2016
Oregon Health & Science University, Portland, OR

- Planned and conducted behavioral tests in mouse model of Alzheimer's dementia and diabetes
- Onboarded and trained interns on procedures
- Assisted with management of IRB and IACUC protocols
- Monitored animal health and breeding schemes in mouse colony
- Performed PCR, immunohistochemistry, and other wet lab procedures
- Reduced, analyzed, and presented data using Excel, SPSS, and GraphPad Prism
- Contributed to building cancer repository by abstracting data from medical records on EPIC

GENETIC COUNSELING EXPERIENCE

Intern, Metabolic/Research Genetic Counseling — September – December 2020
National Human Genome Research Institute, Bethesda, MD (Remote) — *Supervisor: Jen Sloan*

Intern, Cancer Genetic Counseling — September – October 2020
Baltimore Washington Medical Center, Glen Burnie, MD (Remote) — *Supervisor: Rachel Gore*

Intern, Neurology Genetic Counseling — March – August 2020
Johns Hopkins Medicine, Baltimore, MD (Remote) — *Supervisor: Weiyi Mu*

Intern, Cancer Genetic Counseling — October – December 2019
***National Cancer Institute*, Bethesda, MD** — *Supervisors: Grace Fasaye, Alex Lebensohn*

Intern, Pediatric/General Genetic Counseling — September – October 2019
***Johns Hopkins Medicine,* Baltimore, MD** — *Supervisors: Kelsey Guthrie, Weiyi Mu, Natalie Beck*

Intern, Pediatric/General Genetic Counseling — June – July 2019
***Inova Fairfax Hospital,* Annandale, VA** — *Supervisors: Becca Miller, Sonia Thomas*

Intern, Laboratory Genetic Counseling — March – May 2019
***GeneDx,* Gaithersburg, MD** — *Supervisor: Tara Hart*

Intern, Prenatal Genetic Counseling — October 2018 – March 2019
***Greater Baltimore Medical Center,* Towson, MD** — *Supervisors: Amy Kimball, Marcia Ferguson*

Undergraduate Intern, Pediatric Genetic Counseling — September – December 2013
***Oregon Health & Science University,* Portland, OR** — *Supervisors: Kory Keller, Karen Kovak*

VOLUNTEER & ADVOCACY EXPERIENCE

CareRing Support Caller — June 2017 – April 2018
***PRS CrisisLink,* Arlington, VA**

- Made outbound calls to clients to provide friendly conversation, social support, and medication/hygiene reminders to older adults and individuals with mental illness and chronic medical conditions
- Provided crisis counseling and referrals on an as-needed basis
- Conducted periodic screening assessments for depression, environmental risks, and abuse

House Host and Translator — December 2014 – August 2016
***Ronald McDonald House Charities,* Portland, OR**

- Oversaw front desk activities, including check-in/check-out, house tours, room access, guest resources
- Collected and filed confidential guest medical records, surveys, referral forms, etc.
- Provided emotional support and conflict mediation to families

SELECTED PUBLICATIONS & PRESENTATIONS

Mulford, A., Cohen, J. S., Fine, A. S., Roter, D., and Erby, L. A. H. (2021, January). *Influence of exome results on caregiver adaptation and representations of neurodevelopmental disorders*. Master's thesis, Baltimore, MD.

Mulford, A. (2019, May). *Laboratory Genetic Counseling Assistants: The GeneDx Experience*. Presented to staff at GeneDx, Gaithersburg, MD.

Mulford, A. (2019, February). *Reflections and Outcomes from Carrier Testing in Adolescence.* Presented at post-case conference at National Human Genome Research Institute, Bethesda, MD.

Giorgi, J. and **Mulford, A.** (2018, March). *Transitioning Into Summer: Finding Camps for Children with Special Healthcare Needs* (pp. 19-21). Exceptional Parent magazine.
https://reader.mediawiremobile.com/epmagazine/issues/202970/viewer?page=21

Mulford, A. (2018, January). *2018 Newborn Screening Resources* (pp. 28-33). Exceptional Parent magazine.
https://reader.mediawiremobile.com/epmagazine/issues/202720/viewer?page=29

Mulford, A. and Bonhomme, N.F. (2017, September). *Detección en Recién Nacidos: Creating an Outreach and Education Strategy for Engaging Spanish-Speaking Families in Newborn Screening.* Poster session presented at Newborn Screening and Genetic Testing Symposium, Association of Public Health Laboratories (APHL), New Orleans, LA.

Mulford, A. (2017, August). *From Screening to Storytelling: One Mom's Advocacy Journey* (pp. 19-21). Exceptional Parent magazine. https://reader.mediawiremobile.com/epmagazine/issues/201647/viewer?page=21

Johnson, L.A., Zuloaga, K.L., Kugelman, K.L, Mader, K.S., Morre, J.T., Zuloaga, D.G., Weber, S., Marzulla, T., **Mulford, A.,** Button, D., Lindner, J., Alkayed, N.J., Stevens, J.F., Raber, J. (2016, January). *Amelioration of Metabolic Syndrome-Associated Cognitive Impairments in Mice via a Reduction in Dietary Fat Content or Infusion of Non-Diabetic Plasma* (pp. 26-42). EBioMedicine. DOI: http://dx.doi.org/10.1016/j.ebiom.2015.12.008

SKILLS, CERTIFICATIONS, & AFFILIATIONS

- Full professional proficiency in Spanish language
- Certified in ASIST (Applied Suicide Intervention Skills Training), trained on crisis hotline – January 2017 to present
- Student member: Maryland and DC Society of Genetic Counselors – January 2019 to present
- Student member: National Society of Genetic Counselors – March 2019 to present
    - Neurogenetics SIG
    - Student/New Member SIG
    - Psychiatric SIG